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'THREE MONTHS' COLIC'

BY

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(RECEIVED FOR PUBLICATION JANUARY 15, 1954)

In the first three months of life, rhythmic attacks of screaming, which are almost entirely confined to the evenings and cannot be explained by any of the known causes of crying, are a troublesome complaint which is familiar to all who are concerned with the care of well babies. It is commonly called 'three months' colic', because it gets better by the age of 3 months. For the sake of brevity I shall henceforward term it 'colic'.

This paper sets out to marshal the known facts about the condition, to discuss the theories as to its possible causes, and to present for comparison an analysis of data concerning 50 babies who suffered from it and 50 babies who did not.

Description of the Condition

The typical story is that of a baby aged between 3 days and 3 weeks who develops violent screaming attacks in the evenings, usually between 6 p.m. and 10 p.m. He behaves normally during the day, and sleeps well at night apart from demanding the usual night feed. In the attacks his face flushes, his brow furrows, and then he draws his legs up, clenches his fists and emits piercing, high-pitched screams, which do not stop when he is picked up, continuing unabated in his mother's arms. Each attack lasts five minutes or more. As the attack passes off he relaxes and stops screaming, and he is placed in his cot, obviously tired out. He is just about to go to sleep when another attack occurs. The attacks occur at regular intervals, with only a minute or two between them, until 10 p.m. or so, when he falls asleep and has no further trouble until the next evening.

During the attack it is commonly noted that there are unduly loud borborygmi. Some relief is usually given by placing him in the prone position, and he obtains considerable relief by passing flatus per rectum or by having a motion. Most babies obtain relief by sucking at the breast, but a few minutes afterwards the attacks begin again.

Mothers are very liable to take such a baby off the breast on the grounds that the breast milk is not suiting the baby, only to find that the complaint continues unabated when he is fed on cow's milk. They are apt to feed the baby almost constantly, because they ascribe the screaming to hunger, and he seems to obtain some relief from sucking. They are apt to offer him a bottle feed after or instead of a breast feed, only to find that he is no better or refuses it.

There are all gradations in the severity of this condition. Severe attacks cause a great deal of anxiety and alarm. In mild forms there is merely slight irritability in the evenings, the baby appearing to be 'uncomfortable', but apparently content as long as he is nursed. The description given above corresponds exactly with that given by Brennemann, (1945, 1948), Spock (1944, 1946), Keiter (1938), Levin (1950), Neff (1940), Copeland (1940) and others.

It is difficult to assess with accuracy the incidence of colic in well babies, because of the ease with which it can be confused with other conditions. In 100 consecutive well babies in the follow-up clinic at the Jessop Hospital at Sheffield I saw 21 whom I considered to be suffering from colic.* Jorup (1952) claimed that 30% of 589 children attending a child welfare centre in Stockholm had it, but his description does not conform in many important details with that given above. Rosamond (1921) remarked 'Every layman and every doctor with experience knows about three months' colic. It has happened in nearly every household.' Brennemann (1948) went further, and wrote that 'few babies escape it'. That I believe to be an exaggeration.

Review of the Literature

Considering the frequency and troublesome nature of evening colic, it is notable that comparatively few papers have been written on the subject. I could find no mention of it in three recent paediatric textbooks (Moncrieff and Evans, 1953; Fanconi and Wallgren, 1952; Ellis, 1951). A search of 49 volumes of the Quarterly Cumulative Index Medicus, and the 24 volumes of its predecessor, the Index Medicus, provided 38 references

* Subsequent observation in a larger number of babies has suggested that the figure is too high.

to papers in various languages: all but two of these, which were unobtainable either here or in the United States, have been read in the preparation of this paper. All relevant papers have been included in the reference list at the end of this communication for the sake of others who are interested in the subject, but not all have been specifically referred to in the text, for the theories as to aetiology and treatment are so numerous that the insertion of references after each theory or suggested line of treatment would make this review quite unreadable.

Many writers suggest that there are several possible causes of colic. Higgins (1942), for instance, lists 20 causes. Several writers think that the cause is overfeeding. On the other hand Rosamond (1921) says that the cause is obviously underfeeding, and Keiter (1938) supports him. Several writers suggest that it can be due either to underfeeding or overfeeding, which seems to be contradictory. Some think that it is due to excessively frequent feeds, others to too infrequent feeds, and still more to either fault.

Most workers blame the constitution of the feeds on the ground that they are too rich, too weak, too hot, too cold, contain too much fat, too much carbohydrate or too much protein. Others (e.g., Miller, 1948) think that it is useless to change the feeds. Many workers ascribe colic to allergy, mostly to substances in milk, but possibly to substances in cod liver oil or orange juice. McCleave (1928) thought that it might be due to sensitivity to feathers or horsehair. White (1936) claimed that colic is as much a manifestation of allergy as infantile eczema, and described case histories in which the two coexisted, and cases in which colic was cured by removing the allergen by boiling the milk or using a milk substitute. His description of colic, however, does not conform with that given at the beginning of this paper, for the babies had extreme fretfulness aggravated by feeding, with projectile vomiting and usually diarrhoea, a condition which I have not seen. McGee (1943, 1950) agrees that colic is due to allergy, and claims that the probability that the baby will suffer from allergy can be detected while he is *in utero*, by the occurrence of foetal hiccoughs. He wrote that at least 50% of foetuses who had hiccough *in utero* had colic in early infancy as a result of allergy. He wrote that other symptoms are usually associated with colic—nasal blockage or discharge, rattling sounds in the throat, excessive posseting or vomiting, mucus in the stools, constipation or diarrhoea, perianal irritation, nasal rubbing, papular rash on the face, and other troubles, some of them, one feels, being simply manifestations of the normal child. Shannon (1921a and b), Donnally (1930) and others have shown that certain proteins taken by the mother may pass into the milk and cause symptoms in the child. On the other hand Jorup (1952) and Hess (1940) thought that allergy was not the cause of colic.

A surprising number of writers claim that colic is associated with 'hypertonicity'. These writers include Haas (1918), Copeland (1940), Spitz (1951), Moore (1942), Higgins (1942), Neff (1940), Lippman (1928), Bonar (1935) and Miller (1948). The manifestations of hypertonicity given by these writers include such diverse signs and symptoms as an exaggerated Moro reflex, sharp response to sudden light, vigorous crying when having a bath, tenseness, excessive crying, wakefulness, pylorospasm, vomiting, spastic constipation, diarrhoea, abdominal distension, visible peristalsis, cardiospasm, tetany, overaction of the involuntary muscles, general spasticity or rigidity, the 'ability to support the body on the legs at 6 weeks', and to 'hold the head up almost from birth', the 'ability to grasp objects in the first few days of life', unusual alertness, pruritis ani, poor weight gain and many other conditions. Jorup (1952) describes similar symptoms in his cases. He was impressed by the 'neurolability' of colicky babies, the excessive sensitivity to sound and light, the shortness of their sleep, their general restlessness, their diarrhoea and their excessive sweating. Many other writers associate colic with diarrhoea (e.g., Grulee and Eley, 1948; White, 1929, 1936; McGee, 1950), while others claim that it is associated with constipation (Still, 1927; Current, 1920; McGee, 1950). White (1936) said that all but 40 cases seen by him were of the 'sthenic' or 'broad' type.

The parents have frequently been blamed for causing colic (Moore, 1942; Higgins, 1942; Keiter, 1938; Bonar, 1935; Neff, 1940). It is suggested that they cause colic by picking the baby up too much, by 'bouncing him too much after feeds in an effort to get the wind up', and communicating their nervousness and anxiety to him. Brennemann (1948) thought that colic was in some way connected with fatigue in the mother at the end of the day. Bonar (1935) thought that he could predict from the personality of the parents whether their babies were going to have colic. Spitz (1951) regarded colic as a combination of 'congenital hypertonicity' in the baby with 'primary anxious over-permissiveness' in the mother.

Several workers state that colic either never or very rarely occurs in the maternity unit, and only develops when the baby is taken home (Soto, 1937; Alarcon, 1951; Spock, 1944; Keiter, 1938; White, 1936; Pierce, 1948). Huenekens (1928) states that

when a colicky baby is admitted to hospital the symptoms disappear. These workers ascribe the development of colic when the baby is taken home to mishandling, over-stimulation, excessive picking-up and over-anxiety. Hess (1940) suggested, however, that colic could well be overlooked in hospital. Levin (1950) alone wrote that colic occurs in hospital, and described eight cases which he had seen. He thought that the idea that colic does not occur in hospital can be explained by the failure of the nurses and doctors to recognize it.

The most popular explanation of colic is excess of wind in the bowel, or wind trapped in a loop of bowel. Most workers ascribe the excess of wind in the bowel to swallowing air. Several workers mention the relief given by the passage of flatus, placing the baby in the prone position, or applying pressure to the abdomen. Several others ascribe colic to spasms of the intestine, mostly in association with excess of wind (Keiter, 1938; Miller, 1948; White, 1929; Bonar, 1935). White terms the condition 'vagogenic gastroenterospasm'. Some workers ascribe it somehow to immaturity of the intestine, with imbalance of the autonomic nervous system. Jorup (1952) in careful radiological studies found that there was no excess of wind in the intestine, but that the colon showed excessive propulsive activity. He was impressed by the forceful expulsion of barium given as an enema. He found that attacks of pain corresponded in time with violent contractions of the colon.

Finally, a wide variety of other causes have been given for colic in the young baby. They include congenital malformations of the alimentary tract, inguinal hernia, urethral colic, appendicitis, foreign bodies in the alimentary tract, lead poisoning, anal fissure, imperforate anus, peptic ulcer, 'disease of the gall bladder, respiratory tract or osseous system', congenital syphilis, volvulus, intussusception, renal colic, nasopharyngitis, otitis, pyelitis, 'tension developed *in utero* from a hypothetical uterine handicap or transmitted from a high strung mother's system', hyperacidity, exposure to cold, chilling of the extremities, abdominal binders, fatigue toxins from the mother, tension due to lack of oral satisfaction, acidosis, introversion and accumulation of uric acid in the kidneys.

Suggested lines of treatment naturally reflect the views as to the aetiology. They are outlined here for that reason, and because they throw further light on the opinions as to the cause of colic. Moore (1942), Neff (1940) and others advise that the baby should not be picked up so much, and that he should be handled slowly and gently. Spock (1944) warns that it is useless to change the feed, but numerous workers advocate changes in the frequency, quantity and constitution of the feeds. The changes recommended include an increase or decrease in their frequency, increased or decreased quantities, changes in the protein, fat or carbohydrate content, the use of protein milk, buttermilk, skimmed or evaporated milk, lactic acid milk, removal of the baby from the breast, removal of various substances from the mother's diet, the substitution of banana powder for other sugars, the giving of a warm cereal gruel before feeds, thickening the feeds with cereal and adding barley water or casein derivatives to the feed. McGee (1950) suggests a whole series of changes, each one to be tried for a time: boiling the milk, changing to one of low fat content, giving goat's milk, mull-soy, nutramigen, and finally strained meats, olive oil, sugar and calcium instead of milk. One feels that as colic is a self-limiting disease most babies would be better before all these had been tried.

Many workers advocate the use of atropine, some of them until flushing occurs, and other antispasmodics. Levy and Zweifler (1952) found banthine bromide effective. Jorup (1952) found that methylscopolamine nitrate ('skopyl') relieved the symptoms in all his cases. Others recommend prostigmine, opium derivatives, 'demerol,' phenobarbitone, chloral, sodium bicarbonate, peppermint water, sodamint, tincture of cardamom, magnesium carbonate, 'dill water', bismuth, sal volatile, sulphocarbolate of soda, creosote, papain, nux vomica, salad oil, calcium chloride, calcium gluconate or potassium citrate. McGee (1950) found that a drink of whisky (taken by the baby) was effective. Grulee (1920) suggested that every morning and evening the baby should be given 5 ml. of a liquid culture of active lactic acid bacilli.

Numerous workers (e.g., Brennemann, 1948; Higgins, 1942; Miller, 1948) found that an enema gave prompt relief in attacks. Keiter (1938) recommends that a glycerine suppository should be held in place for 10 minutes before feeds. Others advocate the use of a rectal tube. Another worker recommends dilatation of the anal sphincter. Many workers recommend that all precautions should be taken to reduce swallowing air. Levine and Bell (1950) advocate the use of a dummy or pacifier.

As for the prognosis, only two writers (Sheldon, 1951; Still, 1927) suggest that there is any danger in colic: they wrote that it may lead to convulsions. Spock (1949) rightly points out that a baby with colic may become so used to being picked up because of pain in the evenings that he develops a habit of expecting to be picked up: crying in the

evenings therefore persists long after all pain has stopped. McGee (1950) states that throughout life many of these children are poor vegetable eaters, and are finicky with their food. When they begin to go to the kindergarten they will miss a lot of school because of colds, bronchitis, nausea, vomiting, abdominal pain, headaches or fatigue. At school he says that they have difficulty in keeping quiet and in paying attention, and are apt to molest other children. He gives no evidence for these statements. Jorup (1952) says that they later prove to be difficult to wean. They are afraid of strangers. They suck their thumbs or bite their nails. They have a tendency to diarrhoea or to spasms of colic. He did not, however, study controls in whom the incidence of those complaints could be compared.

Such is the literature about colic. The clinical descriptions given by Spock (1946) and Brennemann (1948) are excellent, but I have found no paper which compares colicky babies with others, or which describes a controlled investigation of its treatment. The paper by Jorup (1952) is the only one which really studies colic in some detail, and which has included radiological examination, but, as stated above, the babies which he described had symptoms and signs which are different from those described in this paper.

The Present Study

Method. Data were collected about 50 consecutive babies in the first three months of their life who were said by their mothers to have violent, rhythmical, screaming attacks which did not stop when they were picked up, and for which no cause, such as underfeeding, could be found. Mild cases were excluded, because of the ease with which a wrong diagnosis can be made. The babies were seen in the follow-up clinic for well babies at the Jessop Hospital for Women, Sheffield. Almost all babies are first seen in this clinic between the age of 15 and 30 days. In all cases the diagnosis was made at the time of the first attendance. Three or four babies originally included in the investigation were subsequently withdrawn, because their subsequent course suggested that there were causes other than colic which were responsible for the screaming attacks. In the great majority of cases the mother complained spontaneously about the attacks, but in a few the diagnosis was established as a result of the direct questions, 'How does he behave during the day?', 'What is he like at night?' Apart from the question, 'At what time do the attacks occur?' there were no other leading questions.

When a baby who satisfied the above criteria for diagnosis was found, a pro forma was filled in, on which numerous details of the baby, his mother, the feeding methods and other relevant data were recorded. A routine examination was performed, including a simple developmental examination, on the lines of that suggested by Arnold Gesell.

For comparison controls were chosen in the following way. Whenever a baby was found to have colic, the next baby seen, provided that he had no colic or excessive crying, was used as a control, and a control pro forma was filled in. If two consecutive babies had colic, the next two symptom-free babies were used as controls. In a sense, therefore, both groups were selected, but they were only selected on the grounds of having definite colic of quite severe degree, or of having no colic or anything like it. In all other senses they were unselected and therefore strictly comparable. It should be pointed out, however, that the babies seen at the Jessop Hospital are not representative of the general population, in that the mothers are usually primiparae or have some complication of pregnancy.

It is unfortunate that one has to rely largely on the mother's story for a study of this nature. One is not justified in admitting babies (with their mothers) to hospital for evening colic because the condition is a self-limiting one, because of the risk of infection, and for domestic reasons. It was difficult to obtain x-ray studies, because it was felt that x-ray examination should only be done at the time of the colic, and this necessitated evening visits, often from a considerable distance. X-ray studies were carried out in the evenings, however, on seven severe cases, thanks to the cooperation of the mothers, the radiologists and the radiographers. These radiographs were taken during the attacks of colic. Straight radiographs were followed by a barium enema.

For the purposes of assessment of the straight radiograph a radiographer was asked to pick out at random radiographs of seven babies under 3 months of age, taken for non-abdominal conditions (mostly upper respiratory tract infections), and which included the abdomen on the x-ray film. The radiographs of the babies with colic were then mixed with these. A radiologist (Dr. T. Lodge) then examined the films without knowing the names or condition from which they were suffering and graded them according to the amount of gas in the intestine.

All babies were seen by me personally, and followed up by me, as far as possible up to the age of 6 months. There were 50 babies in each series, and they were seen in the course of one year.

Results. Table 1 shows that there was no significant difference between the two groups with regard to the age of the mother, her parity, the incidence of illnesses during pregnancy, the incidence of foetal 'hiccoughs', the family history of allergy, the sex or birth weight of the baby, the number of feeds per day or the incidence of posseting or vomiting. Slightly more babies in the colic group (44 out of 50) were fully breast fed when first seen, as compared with the control group (35 out of 50). This probably explains the fact that 13 of the babies in the colic group had a motion less frequently than once a day, as compared with five in the control group, for many breast-fed babies have infrequent motions. There was no suggestion of diarrhoea in any of the colic group, which is interesting in view of the often repeated statement that all or most of the babies with colic have diarrhoea.

One child with colic developed mild eczema compared with four in the control group. This figure is not accurate, for not all babies were followed up until 6 months. There was certainly no greater incidence of eczema or other allergic conditions in the babies with colic.

The weight gain between the time of discharge from hospital and the first attendance in the follow-up clinic averaged 9·3 oz. per week in the colic group and 7·7 oz. in the control group. Nineteen babies in the colic group and 19 in the control group were 5% or more above the expected weight when first seen in the follow-up clinic. Thirty-five babies in the colic group and 32 in the control group were up to the expected weight. Six babies in the colic group and nine in the control group were 5% or more below the expected weight.

Table 2 gives further data about the babies with colic. In 33 of the babies the colic developed in the first 10 days during the stay in hospital. In 44 babies it developed in the first 15 days. In no case did a child develop colic after being seen on the first visit in the follow-up clinic. In those who had

TABLE 1

COMPARATIVE DATA ON MOTHER AND CHILD

	Colic Group*	Control Group*
Mother		
Age of mother (in years)		
Mean	27·2	27·1
	σ5·2	σ5·7
Unknown	1	1
Multiparae	13	15
Pre-natal pre-eclampsia or toxaemia	4	4
Hypertension	4	2
Haemorrhage	1	0
Other illnesses, excluding vomiting	3	2
Pre-natal foetal 'hiccoughs'	5	6
Family history of allergy		
Mother or father	7	7
Uncles or aunts	2	3
Grandparents	1	2
Baby		
Male	25	27
Female	25	23
Birth weight (lb. oz.)		
Mean	7·3	7·6
	σ1·0	σ1·3
Method of feeding (at first follow-up visit)		
Fully breast fed	44	35
Complementary feeds	2	5
Artificially fed	4	10
Number of feeds per day (at first follow-up visit)		
Mean	5·6	6
	σ0·7	σ0·7
Posseting or vomiting	22	18
Number of stools per day (at first follow-up visit)		
Mean*	2·8	3·0
	σ3·1	σ1·9
Allergy (eczema, etc.) in first 6 months	1	4
Weight gain since discharge (oz. per week) up to first visit		
Mean	9·3	7·8
	σ3·3	σ3·5
Percentage by which actual weight exceeds expected weight†		
Mean	3·7%	2·3%
	σ8·2%	σ8·2%

* Fifty cases in each group. No record in one colic case.

† The expected weight was obtained by adding 1 oz. for each day of life to the birth weight and subtracting 10.

TABLE 2

DATA CONCERNING COLIC

	No. of Cases
Age of onset of colic	
0 to 5 days	14
6 to 10 days	19
11 to 15 days	11
16 days or more	6
Time of colic	
Any time of day or night, worse in evening	3
5 p.m. to 10 p.m.	1
6 p.m. to 8 p.m. or 9 p.m.	6
6 p.m. to 10 p.m.	21
6 p.m. to 11 p.m. or 12 p.m.	6
7 p.m. to 8 p.m., 9 p.m. or 10 p.m.	3
8 p.m. to 9 p.m., 10 p.m. or 12 p.m.	3
9 p.m. to 12 p.m.	3
10 p.m. to 1 a.m. or 2 a.m.	3
11 p.m. to 12.30 a.m.	1
Effect of a feed	
No difference	3
Feed refused	4
Not tried	4
Colic eased	39
Age of disappearance of colic. Average (43 babies)	9½ *weeks*
Disappearance by end of 2 months	54%
3 months	85%
4 months	100%

not had colic while in hospital, symptoms developed within a week of going home.

In all cases the colic occurred in the evening, but in eight cases it occurred at other times as well, although in them the symptoms were much worse in the evening. In five of them symptoms occurred at other times of the day only on odd occasions. The time of onset of the colic is interesting (Table 2). In 47 of the 50 babies it began at 5 p.m. or later, usually 6 p.m. These times refer to the time of onset as given by the mother at her first attendance in the follow-up clinic. In a few cases the time of onset shifted as the baby grew older. The duration of the colic, with the exception of those three who had colic earlier in the day as well, averaged 3·7 hours when the baby was first seen: the range was one to six hours.

In 39 babies the colic was eased by a feed, in almost all cases only for a short time (10 to 30 minutes). Four babies refused feeds when suffering from colic; three were not helped; in the remaining four feeds were not offered at the time.

The average age at which the symptoms of colic disappeared was 9½ weeks. Approximately two out of five babies lost the colic by the age of 8 weeks, four out of five by the age of 12 weeks, and all had lost it by 16 weeks.

X-ray studies were carried out on too small a number of babies for any firm conclusions to be drawn. Five of the seven babies with colic and one control baby were regarded as having a normal intestinal gas content: two babies with colic and three controls showed a slight increase of gas ('Grade I'). None of the colic babies but three of the controls showed a large amount of gas ('Grades 2 and 3'). All we can say with certainty was that in those seven babies with colic at the time of the x-ray studies there was no evidence of excess of gas in the intestine.

Barium enemas gave no definite information. In three of the children the radiograph showed a loop of redundant sigmoid curling over into the right iliac fossa, but this is known to be common in normal babies at this age. This matter is being investigated further. It is true that the barium was not well retained, as Jorup (1952) found, but we did not feel that the babies with colic were different in this respect from other babies. It was not possible to demonstrate any local obstruction to the passage of gas, but it is possible that further studies will throw light on this.

The Causes of Crying and Colic

One gains the impression from many papers that colic is regarded as practically synonymous with crying. It is very common, however, to see screaming attacks in the evenings in young babies, without any of the known causes of crying being discoverable. The screams are those of pain; they do not stop when the child is picked up; they are rhythmical, suggesting an intestinal origin; they are not due to hunger. This is the picture of the severe case of colic, and nothing can really be confused with it. The mild form, however, can be indistinguishable from other causes of crying, and any diagnosis of colic can be only a matter of opinion: it can only be made in those cases by excluding other causes, by giving, for instance, extra feeds in the evening in order to make sure that the crying is not due to hunger.

Principal Suggested Causes of Colic

Underfeeding. The effects of underfeeding may be indistinguishable from mild colic, except by the relief of symptoms when the underfeeding is corrected. The crying of hunger, like that of colic, is not relieved by picking the baby up: the baby obtains relief, like the colicky baby, by sucking; and in the case of the breast-fed baby the hunger may be only in the evening, for it is common for the milk supply to fall off in the late afternoon and early evening, being perfectly adequate at other times of the day. Not even an average weight gain excludes the possibility of hunger, for there may be sufficient milk in the rest of the day to ensure an average weight gain. But an average weight gain is not necessarily an optimum one for the child in question. When a baby is gaining 12 oz. a week, he is likely to cry a great deal if his feeds are cut down so that his weight gain is merely average. A further snare in the diagnosis lies in infrequent visits. When a baby, for instance, who is seen after an interval of three weeks has gained 21 oz. in that period, it is impossible to be sure that the weight gain has been uniformly distributed within that period: he may have gained 9 oz. in each of the first two weeks and only 3 oz. in the third week. Of course if the weight gain is better than the average it is extremely unlikely that hunger is the cause of crying. It should be noted, however, that the crying of hunger is different from the high-pitched scream of pain. When in doubt test feeding should be carried out in the breast-fed baby, and in case of need a complementary feed, or in a bottle-fed baby, a bigger feed should be given to determine whether it will relieve the symptoms.

I feel that the results of this study show conclusively that colic in our cases was not due to underfeeding. The weight gain in 49 of the 50 cases had been over 5 oz. per week in the interval between

discharge and the first attendance at the hospital—at a time when colic was severe: in 35 of the 50 the weekly weight gain was over 7 oz. and in 19 over 10 oz. Thirty-five of the babies were above the expected weight when first seen. More important still, the weight gain was on the whole greater in the colic series than in the control group.

In eight of the babies who started to have colic in the first week while still in hospital, test feeds were carried out on the seventh day, and in all cases the results indicated an intake of milk which seemed adequate in relation to the weight. The average quantity of milk obtained in the evening feed at the time of colic was 3·1 oz. Test feeds were carried out in four older babies who had colic, and in all of them the quantity obtained in the evenings seemed to be satisfactory.

In all children in whom the weight gain was defective, the food intake was increased. In those who were fully breast fed, this was achieved by expressing milk after every feed, in order to empty the breast better and so to stimulate milk production, and if this failed, complementary feeds were given. Yet in none of the children who were given complementary feeds in this way, and in none of the five who were changed entirely on to artificial feeds, was the colic in any way affected in spite of a considerable increase in the weight gain. The mothers of 10 babies took it on themselves to offer a bottle during the attacks of screaming: four of the babies refused to take the feeds, none of the other six were eased by the additional feed, and after two or three attempts the bottle was not offered again. It was striking that in nine babies in the control series in whom the weekly weight gain by the time of the first attendance had been below 5 oz., there had been no complaint of crying. In some of these children the weight gain had been grossly defective, in three being less than 2 oz. per week. It is a well known fact that underfeeding is by no means always accompanied by excessive crying. It is obvious that underfeeding, at least without some additional factor, does not cause evening colic.

Overfeeding. I firmly believe that for practical purposes overfeeding in a young baby is a myth. It is so rare that one can truthfully say that it practically never occurs.

It is true that the average weight gain in the colic series tended to be very slightly more than that in the control series, but the difference was not of statistical significance. Twelve of the controls were gaining more than 10 oz. a week, and yet did not have colic. Furthermore in 16 of the colic babies in whom the weight gain by the time of the first attendance had been much above the average, the weight gain rapidly fell in the ensuing four weeks without alleviation of the colic.

The number of feeds per day was almost exactly the same in the two groups.

Allergy. Our data give no support to the theory that the cause of colic is allergy. There was a family history of allergy in 10 babies in the colic group and in 12 in the control group. One baby in the colic group developed eczema compared with four in the control group. As for McGee's theory concerning foetal hiccough, five mothers of the colic babies gave a history of sudden, rhythmical, jerky movements in the foetus, simulating hiccoughs as compared with six mothers of babies in the control group. In the five babies who were taken off the breast because of insufficiency of milk and given cow's milk, the colic continued unabated not only when the breast milk supply fell off but when cow's milk was substituted.

All mothers who were breast feeding babies suffering from colic were asked whether any food which they were taking had a bearing on the colic. Only seven mothers answered in the affirmative, blaming grapefruit, tomatoes, sprouts, peas, beans, onions, turnips and bananas. Only one of those foods was blamed by two mothers, namely peas. It is doubtful whether any of them were really to blame, for the colic persisted even though these substances were excluded from the mother's diet.

Hypertonia. I was quite unable to find any of the so-called signs of hypertonia in the babies with colic. The muscle tone, head control and general development seemed to be identical in the two groups, both in the newborn period and when followed up to the age of 6 months. It is unfortunately not possible to translate these findings in the young baby into figures.

It was possible, however, to compare numerically the incidence of posseting or vomiting and the frequency of stools in the two groups. There was no significant difference. I have never seen 'diarrhoea' in a baby with colic, though there is no reason why it should not occur as frequently in babies with colic as it does in other babies. I have seen no evidence of 'spastic constipation' in babies with colic. In fact I have never seen any abnormality of the bowels in these cases.

I have not seen any of the other signs of hypertonia mentioned by writers, except those which can only be regarded as normal, such as 'vigorous crying when getting a bath'.

Gastric or Colonic Flatulence. Gastric flatulence ('wind') may be due to sucking too long on the breast, gulping the milk down too quickly as a result of an unduly rapid flow of milk from the breast, or, if the baby is bottle fed, from having too small a hole in the teat, from allowing him to suck when the teat has become flat as a result of a vacuum, from failure to tilt the bottle sufficiently to keep the teat full of milk, or from allowing him to suck when the bottle has been emptied.

Although excess of wind in the stomach causes screams of pain during or immediately after a feed, it does not cause rhythmical attacks of crying for several hours, which are not relieved by picking the baby up. If a baby with wind is picked up, the wind is likely to be expelled and the pain relieved.

The possibility that 'colic' is due to the passage of swallowed wind into the intestine is not so easy to discard. It is commonly supposed that most wind in the bowel is the product of fermentation and bacterial action, but it is difficult to say how much wind comes from the stomach. I do not think that adult air swallowers have an excess of wind in the bowel. It is well known that babies swallow air as a result of the various errors of feeding technique which have been mentioned, but I have not seen evening colic occur in such babies. The limited number of x-ray studies which we were able to make in our cases did not show any excess of gas in the intestine, and that was the finding of Jorup (1952). There is therefore no evidence of excess of wind in the intestine of colicky babies.

That wind in the colon plays a part in the production of symptoms is strongly supported by the fact that attacks of colic are nearly always relieved by the passage of flatus or a stool. I have repeatedly observed attacks relieved in this way. Many workers, furthermore, have found that attacks are relieved by enemas. It would seem that an additional factor is necessary, probably of the nature of spasmodic contractions or kinking of the bowel. This is supported by the observation by myself and by many mothers that during an attack borborygmi are particularly noticeable. Mothers say that they hear the wind rumbling round.

It would seem doubtful whether immaturity of the autonomic nervous system is a factor, for one would expect that if that were the case colic would be commoner in premature babies, which it is not. (Three babies in the colic group and four in the control group were born prematurely. The incidence of premature births in the Jessop Hospital is approximately 8%.) Pierce (1948) made the interesting observation that colic may begin later in premature babies than in full-term ones. I have seen this once only (in a baby seen after this series was completed). Confirmation of this is required.

Spoiling. One of the arguments adduced by several workers who ascribe colic to 'spoiling' is the statement that colic only begins when the mother gets home, and finds herself on her own without the moral support of the hospital staff. But in 33 out of 49 of our cases the colic began while the mother and baby were in hospital. It should be noted that at the Jessop Hospital babies are kept at the mother's bedside and can be picked up by the mother as often as she wants, and they are fed on a self-demand schedule. Some would call this 'over-permissiveness', but this is a matter of opinion. We commonly diagnose colic in babies during their stay in the Jessop Hospital, confirming the diagnosis by their subsequent course.

Analysis of other data, such as the age of the mother and her parity, which might have an indirect bearing on her liability to spoil her child, threw no light on the problem, for the data for the two groups were the same. Though only one child in a family may be spoiled, it was noted that not all children in a family suffered from colic, there being a history of colic in another sibling in three of the 11 babies in the colic series, who were not first born. No siblings of the 15 comparable babies in the control group had colic.

It is difficult to understand why rhythmical attacks of screaming, which do not stop when the baby is picked up and such as only occur with pain, should be ascribed to 'over-permissiveness' on the part of the mother, spoiling and other forms of mismanagement, yet many writers consider this to be an important cause of colic. Any parent who has possessed a child with colic knows that it is a most worrying and disturbing complaint, and that a baby with obvious pain has to be picked up and cuddled. Only a thoroughly hard-hearted mother, or a mother who has been foolish enough to listen to advice that a baby should never be picked up when he cries because of the risk of spoiling him, would leave him to cry without picking him up. As Spock (1949) pointed out, a baby may come to expect to be picked up in the evenings as a result of what has happened when he had pain, and the attacks of colic are then slowly and imperceptibly replaced by crying from habit. It is difficult to say where one ends and the other begins. The mother has to be guided by the nature of the cry, together with the fact that it is most unusual for true colic to continue after 3½ or 4 months. This spoiling is the result, not the cause, of the colic.

Though severe attacks of colic could hardly be

mistaken for the mere desire to be picked up and loved, mild attacks could very well be so mistaken. It is quite possible, and indeed likely, on the one hand, that very mild discomfort in the evening would be enough to awaken a baby or keep him awake, but not enough to cause him to cry when in his mother's arms. On the other hand, it is common for young babies to sleep well during the day and night, but to regard the evening as a time for play. They are most wide awake then, and demand attention. Such babies are apt to be called naughty or spoiled but in fact they merely want love and attention, having been asleep all day. Mothers who rightly pick such babies up and play with them are apt to be considered to be over-anxious or to be mismanaging them. This rhythm of evening activity is only temporary.

An intelligent older baby, from 2 months onwards, frequently cries from boredom, or from the desire for company. Such babies cry if left alone, but are perfectly content when in the presence of others and able to see what is going on without being picked up or being given attention. Ignorance of this fact leads many mothers to think that their baby has wind or colic, when in fact all he wants is to see what is happening. No baby with anything but the mildest colic would stop crying merely by being brought into the presence of others.

Desire for More Sucking Experience. There is no doubt that babies with colic are eased when they suck, and for that reason many babies with colic are given almost continuous breast feeds in the evenings. One mother said, 'She always seems to want feeding in the attacks, but when given the breast she doesn't take it: she just seems to want something in the mouth.'

Many mothers have told me how sucking seemed to afford some relief, and I have seen this myself. Levine and Bell (1950) for this reason advocated the use of a dummy or pacifier for babies with colic. The fact that sucking causes relief, however, does not prove that the cause can be found in a desire for further sucking experience.

We observed one baby with colic when under the x-ray screen, and could not detect any change in the gas pattern in the bowel when sucking was allowed. It is difficult to understand why babies obtain relief in this way.

Organic Causes. Though several writers have suggested that colic may be due to organic disease, especially intestinal obstruction, it is difficult to see how these conditions may be confused, except perhaps on the first day on which the colic occurs. The regular attacks of pain every evening could hardly be due to obstruction.

Other Causes of Crying. There are many other causes of crying in young babies which can well be confused with colic. If a baby cries when returned to his cot after a feed, he is apt to be thought to have colic, though this crying may be due to wind or other causes.

A baby may feel hungry when he brings his wind up after a feed, and demand more milk. He may awaken and cry for food an hour or two after a feed even though there is enough breast milk if he is caused to suck longer than he needs on the first breast before being transferred to the second, for that will make him tired and he will go to sleep before he has had enough milk from the second breast. He goes to sleep, in other words, because he is tired, and not because he has had sufficient milk to put him to sleep. A baby may cry after a feed because he does not want to leave his mother's arms, because the light is put out, because he has wetted or soiled his napkin, or because he is uncomfortable from overclothing. Most babies cry when they are tired. All these causes of crying have to be eliminated before the diagnosis of colic can be made.

Purgatives Taken by the Mother. It has been suggested that colic in breast-fed babies is the result of constipation. There is disagreement (Illingworth, 1953) as to whether purgatives of the anthracine group (senna, cascara, rhubarb and aloes) can affect the baby, but some consider that they may. However only four of the 50 mothers of colicky babies were taking these purgatives, as compared with three in the control group.

Discussion

I believe that there is strong evidence that colic is not caused by underfeeding, overfeeding, errors of feeding technique, mismanagement, allergy, substances taken by the mother or swallowing air. I do not think that it is due to an excess of wind in the intestines. I have never seen any evidence that colic is associated with hypertonicity or with any particular type of baby or parent. The outstanding impression given by the colicky baby, except in the evening, is that he is a well, happy, thriving, well fed and well managed baby with nothing wrong with him. His stools are normal; he may posset, but he does not posset more than any other baby. He grows up to be a nice normal child in no way different from other children.

The most likely explanation of the attacks lies in a localized obstruction to the passage of gas in the colon by spasm or kinking of uncertain cause. This

explanation alone explains the excessive borborygmi, the relief by the passage of flatus or of a stool, the relief by an enema, together with the absence of radiological evidence of an excess of gas in the bowel. The rhythmical attacks of abdominal pain at constant short intervals is typical of a pain of intestinal origin. It seems that the main hope of elucidating the cause of colic lies in further radiological studies of babies—both of sufferers and non-sufferers. Such studies are in progress, and it is hoped that they will form the subject of a further communication.

Further light may also be thrown on the condition by a study of the response to antispasmodic drugs; a controlled investigation into the effect of methylscopolamine nitrate is in progress at the Jessop Hospital.

I cannot suggest any reason for the predominant occurrence of colic in the evenings.

Summary

The term 'three months' colic' is reserved for a clinical entity in which the baby, in the first three months of life, has rhythmical screaming attacks in the evenings, which are not stopped when he is picked up, and for which there is no obvious explanation, such as hunger. The great ease with which crying can be ascribed to colic when in fact it is due to some readily correctable cause such as hunger is emphasized. Severe forms, however, are felt to be so characteristic that they cannot be confused with anything else. The literature on the subject is reviewed.

A controlled investigation of colic was carried out, 50 babies with colic being compared with 50 who had no colic. It is shown that the mothers of these two groups of babies differed in no way as regards their age, parity or pregnancy history. The babies differed in no way as regards their sex, birth weight, feeding history, family history of allergy, signs of allergy, incidence of posseting, number of stools, or weight gain. They appeared to be well, normal babies apart from their attacks of pain in the evenings, and when followed up they continued to be normal.

In 33 out of 49 babies the colic began in hospital. In 44 of the babies it began in the first 15 days. In 47 of the 50 babies it began at 5 p.m. or later in the evening. The average age at which the colic disappeared was $9\frac{1}{2}$ weeks. Fifty-four per cent had lost it by the end of two months, 85% by the end of three months, and all by the end of four months.

The cause of colic, in the light of the above findings, is discussed. It is felt that it is not due to underfeeding, overfeeding, or other errors of feeding technique. It is not due to mismanagement or spoiling, to allergy, hypertonia, swallowed air or to foods taken by the mother.

X-ray studies taken during an attack of colic did not show an excess of gas in the bowel. The most likely explanation of colic is thought to be the local obstruction to the passage of gas in the colon by local spasm or kinking of uncertain cause.

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IMMUNIZATION OF INFANTS WITH TRIPLE ANTIGEN

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The number of inoculations received by infants has reached formidable proportions. To minimize the number of injections required to produce full and effective immunization is one of the aims of all who are responsible for the prevention of disease in children. In recent years the efficacy of immunization procedures against diphtheria, tetanus and whooping cough has become apparent. The desirability of protection against diphtheria and whooping cough is accepted, but there are many who now believe that tetanus should be included, particularly in view of the fact that the deaths from tetanus in persons under 20 years of age in England and Wales number about 30 a year.

Our aim in this investigation was to demonstrate that infants of 3 months of age can be effectively immunized against diphtheria, tetanus and pertussis by the administration of a combined prophylactic. The literature contains favourable reports, particularly from the U.S.A., on the successful immunization of infants with a combined vaccine (di Sant'Agnese, 1947; Peterson and Christie, 1951). Earlier reports give evidence of successful protection conferred on young infants against pertussis and diphtheria, particularly when an adsorbed antigen has been used (Sako, Treuting, Witt and Nichamin, 1945; Bell, 1948; Kendrick, 1943).

It should be stated at the outset that in this trial no investigations were carried out on the antibody content of the infants' blood before immunization.

We used a combined antigen adsorbed on aluminium phosphate, in view of the reports (Sako *et al.*, 1945; Sauer, 1946) that aluminium hydróxide adsorbed antigens give a better immunity response in infants than do plain suspensions of bacterial and fluid toxoids. The results of our subsequent investigations, in which we used unadsorbed prophylactics, will be reported.

The triple antigen used in the present trial contained 25 Lf. diphtheria toxoid, 2·5 Lf. tetanus toxoid and 20,000 million *H. Pertussis* organisms with the addition of 5 mg. of aluminium phosphate to the millilitre.

The infants were selected from those attending the clinic of the University Department of Child Health held at St. Mary's Hospital, Manchester. The only criteria for inclusion in the scheme were that the infant was healthy at the time of inoculation and that there was no family history of epilepsy or convulsions in childhood. To date 200 infants have been immunized.

The first injection (0·5 ml.) was given at the age of 3 months, the second (0·75 ml.) a month later and the third (1·0 ml.) four to five months after the second. The reason for delaying the third injection was to use this as a 'booster' before the child became exposed to the extra risks of infection during the second year of life.

The antigen was given intramuscularly, deep into the upper and outer quadrant of the buttock, alternating the side used at successive injections to avoid superimposition. After drawing up the fluid in the syringe a fresh needle was used to ensure that none of the vaccine was injected into the subcutaneous tissue (which might be a possible cause of abscess formation). Similarly the leakage back along the track of the injection was minimized by inserting the needle obliquely.

Local reaction was common in the form of oedema and erythema, lasting sometimes for two or three days, but usually for no longer than 24 hours. In one case a local abscess formed in the subcutaneous tissue; the aspirated fluid was sterile on culture. One aspiration sufficed to effect a cure.

Some degree of constitutional upset was noted in many infants. Fretfulness for a few hours after the injection was the most common and in a few persisted for two days. Some vomited one or two feeds after their inoculation, but soon recovered and then fed satisfactorily. Drowsiness, for up to 12 hours after the injection, was occasionally reported. This had been noted much more frequently in a series of newborn infants immunized against pertussis (to be published) and did not seem to be a contraindication to further inoculation. Similarly, some mothers had remarked on the somnolence of

their infants following diphtheria immunization alone. In only one case so far has it been thought necessary to discontinue the course of immunization and in this case the infant was stated to have vomited and been fretful for five days after the second injection.

An interesting complication, if such it be, remarked by one mother, was the occurrence of a harsh, barking cough beginning about four days after the injection and lasting for about a week. This had been noted by four or five mothers in the series (consisting of more than a thousand infants) inoculated with pertussis vaccine.

One month after the third injection blood was taken from 35 infants in order to assess the antibody content, i.e. diphtheria and tetanus antitoxins and *H. pertussis* agglutinins. Diphtheria antitoxins were titrated on guinea-pig skin and tetanus antitoxins in mice, according to methods recommended for testing prophylactics in the Therapeutic Substances Act. For the pertussis agglutinins standardized *H. pertussis* rabbit immune serum and antigen were used as controls. The serum was diluted 1 in 8 in saline, doubling over until a suitable end-point was attained. To one volume of the diluted serum in Dreyer's tubes one volume of *H. pertussis* antigen at a concentration of 2,000 $\times$ 10^6 organisms per ml. was added. Test samples of sera were likewise diluted and *H. pertussis* antigen added to each dilution. The tubes containing the diluted serum plus the antigen were incubated overnight at a temperature of 37° C.

Tables 1-4 give the results obtained.

TABLE 1

ANTIBODY TITRES

No.	Pertussis Agglutination Titre	Tetanus Antitoxin (units/ml.)	Diphtheria Antitoxin (units/ml.)
1 ..	<1/16	1·87	1·80
2 ..	<1/16	2·37	3·60
3 ..	1/128	2·37	0·45
4 ..	1/2,000	2·37	4·80
5 ..	1/3,000	>2·50	4·80
6 ..	1/3,000	5·25	11·25
7 ..	1/1,500	No serum	17·50
8 ..	1/1,500	2·37	8·75
9 ..	1/256	2·37	12·25
10 ..	1/512	7·87	6·75
11 ..	1/1,000	>5·50	8·75
12 ..	1/2,000	5·22	3·60
13 ..	1/4,000	5·50	4·50
14 ..	1/512	No serum	No serum
15 ..	1/2,000	>8·75	7·50
16 ..	1/1,000	>5·50	4·50
17 ..	1/1,500	2·47	6·75
18 ..	1/1,000	1·37	7·50
19 ..	1/512	6·38	7·00
20 ..	1/512	2·62	6·25
21 ..	1/2,048	4·12	8·75
22 ..	1/1,000	>8·75	12·50
23 ..	1/1,500	21·00	15·75
24 ..	1/4,000	>8·75	15·75
25 ..	1/2,500	6·38	7·00
26 ..	1/256	1·3	1·87
27 ..	1/2,048	15·75	8·75
28 ..	1/5,000	7·13	7·00
29 ..	1/2,000	4·38	5·62
30 ..	1/64	1·92	2·62
31 ..	1/3,072	1·31	5·25
32 ..	1/5,000	4·38	3·75
33 ..	1/1,000	2·62	11·25
34 ..	1/2,000	8·75	7·50
35 ..	1/1,000	6·12	5·00

Discussion

In addition to studying the development of antibodies in young infants following the injection of different antigens we also wished to ascertain if

TABLE 2

No. Tested	No. of Children with Diphtheria Antitoxin Level of					
34	<0·5	0·4–1·0	1·0–2·5	2·5–5·0	5·0–10·0	10·0–20·0
	0	1	2	9	15	7

TABLE 3

No. Tested	No. of Children with Tetanus Antitoxin Level of			
33	<1·0	1·0–5·0	5·0–10·0	10
	0	17	14	2

TABLE 4

No. Tested	No. of Children with Pertussis Agglutination Titre of									
35	<1/16	1/16	1/32	1/64	1/128	1/256	1/512	1/1,000	1/2,000	1/4,000
	2	0	0	1	1	2	4	10	11	4

there was any interference or competition between the antigens.

The results indicate a uniformly satisfactory response to tetanus and diphtheria antigens and to 33 out of 35 pertussis inoculations, so that if one accepts the experimental work of Barr and Llewellyn-Jones (1953), suggesting that, unless optimal proportions of diphtheria toxoid and tetanus toxoid are present in a vaccine, antagonism is likely to occur, the proportion of the constituents in this vaccine may be considered good.

The protective level of tetanus antitoxin in man is uncertain, but figures commonly expressed are between 0·01 and 0·1 unit of antitoxin per ml. (Bigler, 1951). In the present series the antitoxin level in all the infants a month after the third injection was far greater.

Vahlquist (1949) states that passively transmitted diphtheria antitoxin levels exceeding 0·1 unit per ml. interfere with active immunization and that levels below 0·02 unit per ml. do not. Barr (1950), by calculating the rate of loss of maternally acquired antibody and assessing the cord blood levels in infants estimated that, in two districts surveyed, 80% of the child population could be successfully immunized at 3 months of age. The level of antitoxin required to produce immunity is considered to be 0·03 unit per ml. All the infants immunized in the series reported in this paper achieved far higher titres, but it is possible that the lower titre in some children may be due to the presence of antitoxin from the maternal circulation before the injection of the vaccine. It seems, therefore, that at this age babies can be successfully immunized against diphtheria, despite the fact that a small proportion of them may still have a certain amount of maternal antibody. From other trials evidence is forthcoming that children with a high titre of maternal antitoxin immunized even at an earlier age than 3 months will acquire a basic immunity to diphtheria, although the level of actively produced antitoxin in their blood may be low. If such children receive booster doses at a later age they will respond with an antitoxin outflow in the same way as will children with no, or only traces of, maternal antitoxin at the time of primary immunization. The antitoxin assessment gives, therefore, a quantitative but not a qualitative evaluation of acquired immunity. The figures in Table 1 would also appear to confirm the view that in a properly balanced mixture of antigens there is no danger of these antigens interfering with each other's action.

Although it cannot be stated that a certain level of agglutinins will ensure partial or complete protection against pertussis, it may nevertheless be regarded as an indication of an immunological response to a bacterial antigen. From field trials conducted in this country it is hoped to learn how far agglutinin levels produced as a response to a vaccine can be related to the degree of protection against pertussis. In our series most children developed an agglutinin titre of 1 in 64 or above which figure we believe to be of certain significance.

In this series of tests we have injected graded doses of the antigen (0·5, 0·75 and 1 ml.) and the children have responded well. It is known, however (Sako *et al.*, 1945), that young babies respond better to adsorbed antigens than to plain fluid antigens. It should therefore be borne in mind, when immunizing young babies, that the doses, particularly the first dose used in the primary stimulus, should be greater when fluid toxoids or plain vaccines are used than when adsorbed antigens are given, in view of the findings of Barr and Glenny (1945), who have shown the importance of the size of the first dose in achieving a satisfactory basic immunity.

From Table 1 it can be seen that some children produced higher titres against pertussis than against diphtheria or tetanus and vice versa. This would indicate that the individual antigenic response to the three components is an independent phenomenon and may vary with each child.

It was not possible, in view of the infrequency of severe reactions, to deduce any relationship between the severity of reaction and the antibody titre.

Summary

In a series of more than 200 infants, antibody response to all three constituents of a triple antigen was satisfactory in those tested.

The reactions were no more severe than those following single antigens.

Because the addition of tetanus does not interfere with the production of diphtheria and pertussis antibodies its inclusion is a useful addition to the routine protection of children.

Thanks are due to Professor Wilfrid Gaisford for his constant encouragement and advice, to Dr. D. G. Evans for his advice, for his cooperation, to Dr. J. Ungar, of Glaxo Laboratories, Ltd., and to that Company, which supplied the triple antigen used in this trial.

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THE VALUE OF HUMAN MILK COMPARED WITH OTHER FEEDS FOR PREMATURE INFANTS

BY

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The food for choice for premature babies is still a matter of much discussion. Some paediatricians believe that human milk is not ideal because of the low proportions of protein and mineral salts and the high proportion of fat. Jorpes, Magnusson and Wretlind (1946) reported better weight gains by adding hydrolysed protein to human milk. The addition of skimmed lactic acid milk to human milk has been suggested by Hess and Lundeen (1949). Other workers have obtained better rates of gain on half-skimmed dried cow's milk instead of human milk (Gordon, Levine and McNamara, 1947; Mackay and Levin, 1953). It has also been suggested that cow's milk is superior to human milk in preventing rickets in premature infants (von Sydow, 1946).

On the other hand it is known that the fat of human milk is better utilized than the fat of cow's milk (Gordon and McNamara, 1941) and the retention and utilization of the available protein is much higher in the premature baby than in larger babies (Gordon and Levine, 1944). In addition, it has been suggested that retrolental fibroplasia is less likely to develop among babies fed on human milk, and to quote Hepner and Krause (1952) 'this has influenced more paediatricians either to continue using, or to revert to using human milk for premature feeding'. These workers found 45% blind babies among 49 fed on a high electrolytic cow's milk diet and only 8% among 84 fed on human milk.

Ford (1949) reported a smaller initial loss and a more rapid return to birth weight among babies fed on human milk than among babies fed on three different cow's milk mixtures. Subsequent rates of gain were similar on all diets. All babies in his investigation were over 3½ lb. (1,588 g.) at birth.

When assessing the value of a diet it is customary to use the rate of gain in weight as the yard stick, but gain in weight varies with the degree of water retention and is not a reliable index of growth. This will be referred to later in this paper. In addition, it has not yet been proved that the maximum rate of growth is the optimum.

Young, Poyner-Wall, Humphreys, Finch and Broadbent (1950) working in the Sorrento Premature Baby Unit and the Birmingham Children's Hospital, studied the nutrition of premature babies by means of serum protein and haemoglobin levels as well as by weight. These workers found that the progress of babies weighing over 3½ lb. (1,588 g.) at birth was unaffected by the various diets used, provided sufficient calories were given, but they suggested that human milk and modified cow's milk with a low protein content similar to that of human milk might not supply sufficient protein for babies weighing less than 3½ lb. (1,588 g.) at birth and that the resulting malnutrition might lead to infection. Their trials included only 10 babies with birth weights less than 3 lb. (1,361 g.) and of the 134 babies the observations on whom were finally analysed, only five were fed on unmodified human milk. During the trials, 31 babies were excluded because of infection, but the diets of these babies were not indicated. One cannot therefore exclude the remote possibility that the diets which gave the least protection against infection gave the best final results because the more weakly babies had been eliminated by infection.

From practical experience of many types of diet used in the Premature Baby Unit at Sorrento, both the nursing and medical staff had the impression that babies fed on human milk not only gave less

anxiety during the early days but also had less subsequent infection and a lower mortality rate. This impression had to be proved or disproved, and it was felt that if morbidity and mortality were studied in addition to serum protein and haemoglobin levels and weight, and if supervision could be continued until the age of 1 year, then the performance of babies fed on human milk could be more fairly compared with that of babies fed on other low- and on high-protein diets and the following questions might be answered: (1) Is there any evidence that unmodified human milk is an unsuitable food for small premature babies? (2) If unmodified human milk should not prove to be the most suitable, should additions be made to human milk or should cow's milk be used instead? (3) Even if the best results are obtained with human milk (alone or with additions) which cow's milk mixture is the best substitute when human milk is not available? (4) If a high-protein diet gives the best results, should part of the protein be hydrolysed?

It was in an attempt to answer these questions that the following investigation was begun. It originally included 164 babies with a birth weight under 4 lb. (1,814 g.). These babies were admitted to the Sorrento Premature Baby Unit from the City of Birmingham and the surrounding areas during the years 1948-1951. On admission, *all* babies weighing less than 4 lb. (1,814 g.) at birth were placed in half-pound birth-weight groups, and in each weight group were allocated in rotation to the five diets (Table 1) but babies were only finally included in the reports if they survived the first week of life. The exceptions were (1) babies with obvious congenital defects; (2) babies admitted after the first 12 hours of life because the exact birth weight was not known; (3) babies in the 3-4 lb. (1,361-1,814 g.) group admitted from outside the City of Birmingham during the last 18 months of the investigation (the number of babies in this group was adequate if local babies only were included and this obviated long journeys to the follow-up clinic); (4) babies in the higher weight groups admitted during the last six months of the trials because a sufficient number had already been investigated.

Of the 164 babies originally included at the age of 1 week, the following had to be excluded at a later stage: (1) Three babies with late-presenting congenital defects (one hiatus hernia, one cystic lung and one hydrocephalus); (2) one baby whose total number of blood samples was insufficient owing to accidents to samples during testing or transit; (3) five babies who died during their stay in hospital, one death being due to atelectasis (17 days), two to pneumonia (17 days and 5 weeks), one to strangulated hernia (16 days) and one to meningitis (6 weeks). These deaths are included in the mortality

TABLE 1

DISTRIBUTION OF BABIES IN BIRTH-WEIGHT AND DIET GROUPS

Birth Weight			A. Human Milk			B. Low-protein Cow's Milk Mixture (Evaporated milk)			C. High-protein Cow's Milk Mixture (Half-skimmed dried milk)			D. Human Milk with Added Protein			E. Low-protein Cow's Milk Mixture with Added Protein		
g.	lb.	oz.	Males	Females	Total	Males	Females	Total	Males	Females	Total	Males	Females	Total	Males	Females	Total
up to 900	up to 2	up to 32	—	1	1	—	—	—	—	—	—	—	—	—	—	—	—
900-1,140	2 to 2½	32 — 40	2	2	4 (3 twins 1 triplet)	1	1	2 (1 twin)	1	2	3 (1 twin)	1	1	2	1	1	2
1,140-1,360	2½ to 3	40 — 48	2	8	10 (1 twin)	4	7	11 (5 twins)	1	7	8	2	4	6 (4 twins, 1 triplet)	2	4	6 (2 twins)
1,360-1,590	3 to 3½	48 — 56	5	7	12 (3 twins, 1 triplet)	4	6	10 (3 twins)	9	5	14 (8 twins, 1 triplet)	9	3	12 (2 twins)	4	7	11 (5 twins)
1,590-1,820	3½ to 4	56 64	4	4	8 (1 twin)	6	4	10 (5 twins)	5	4	9 (3 twins)	2	2	4 (2 twins)	5	2	7 (2 twins)
Total 4 lb. (1,820 g.) and less			13	22	35	15	18	33	16	18	34	14	10	24	12	14	26

rates of the various diet groups, and the cases of infection are included in the infection rates; (4) three babies for whom it was necessary to change the diet, one infant weighing 1 lb. 12 oz. (795 g.) did not tolerate the addition of hydrolysed casein to human milk and two were changed to human milk after having developed severe infections on the low-protein cow's milk mixture. The two with infections are included in the infection rates for the various diets. The remaining 152 babies were grouped according to diet and birth weight as shown in Table 1.

Records

Weight. Babies were weighed naked on admission (to check birth weight) and thereafter twice weekly.

Haemoglobin. Levels were estimated weekly using the Evans electro-selenium photo-electric colorimeter.

Serum Proteins. Levels were determined weekly on serum from venous blood collected from a scalp vein.

Infections. All infections, major and minor, were recorded.

Progress after Discharge from Unit. The infants were seen regularly at a special follow-up clinic at Sorrento Maternity Hospital.

Mortality. All infants were traced to the age of 1 year or to death if this occurred before the age of 1 year. All deaths were known and recorded.

In addition, these babies were included in two other investigations which were also in progress at the time, namely on rickets and retrolental fibroplasia. Because of these investigations the wrists of all babies were radiographed at the age of 3 months, and the fundi of all babies were examined at regular intervals.

Diets and Methods of Feeding

Type of Diet. Five diets were used in this investigation and details are shown in Table 2. In order to ensure that calories would not be lost from inability to utilize high percentages of cow's milk fat, the fat content was kept at 1·6% in the three cow's milk mixtures. The caloric values were all adjusted to 20 per oz. by varying the amount of sugar in the cow's milk mixtures and by slight dilution of the human milk before adding the hydrolysed casein.

Babies fed on human milk (diet A) could be compared with babies fed on human milk reinforced with hydrolysed casein (diet D), a low-protein cow's milk mixture (diet B), a cow's milk mixture with a high content of protein (diet C) and a high-protein cow's milk mixture in which part of the protein was hydrolysed (diet E).

Method of Feeding. The feeding routine was the same for all babies and was that normally employed in the Unit. There was an initial starvation period during which nothing was given by mouth. Feeding began on the third day for babies who weighed 3-4 lb. (1,361-1,814 g.) at birth and on the fourth day for those under 3 lb. (1,361 g.). All the diets were given diluted at first, but full strength was reached by the seventh day in the case of the larger babies and by the tenth day in the case of the smaller babies. The volume of fluid given each day for the first ten days was calculated according to the formula

$$\tfrac{1}{4} \text{ oz.} \times \text{day of life} \times \text{birth weight in lb.}$$

Between the tenth and fourteenth days of life the daily

TABLE 2
COMPOSITION OF DIETS USED IN INVESTIGATION

	Name of Diet	Code	Composition of Diet	Protein (%)	Fat (%)	Carbo-hydrate (%)	Mineral Salts (%)	Calories per Fl. Oz. of Mixture (28·4 ml.)
A	Human milk	o——o	Human milk	1·5	4·0	7·5	0·2	20
B	Low-protein cow's milk mixture (evaporated milk)	●–·–·–●	Evaporated full-cream cow's milk 1 in 5 with 1 drachm(1) sugar to every 1½ oz. of mixture	1·7	1·6	10·3	0·4	20
C	High-protein cow's milk mixture (half-skimmed dried)	●– – – –●	Half-skimmed dried cow's milk 1 in 10 with 1 drachm(2) sugar to every 2 oz. of mixture	3·0	1·6	10·7	0·7	20
D	Human milk with added protein	x——x	Human milk with sweetened casein hydrolysate ('casydrol' benger-genato-san) 7·75 g.(3) to 8·75 fl. oz. of human milk and 1·25 fl. oz. of water	3·3	3·5	6·6	0·4	20
E	Low-protein cow's milk mixture with added protein	x– – – –x	Evaporated full-cream cow's milk 1 in 6 with 2 drachm(4) of sweetened casein hydrolysate and 1 drachm of sugar to every 2 oz. of mixture	2·95	1·6	9·5	0·4	20

(1) 4 g. sugar to 43 ml. mixture.
(2) 4 g. sugar to 57 ml. mixture.
(3) 7·75 g. casein hydrolysate to 248 ml. human milk and 35 ml. water.
(4) 2 g. casein hydrolysate and 4 g. sugar to 57 ml. mixture.

volume was increased to 3 oz. per lb. (200 ml. per kg.). After the birth weight had been passed, the quantity was calculated on actual weight instead of the birth weight.

Supplements. All babies had the same supplements, i.e., Vitamin B, ½ tablet 'benerva' (0·5 mg. B_1 and B_2 and 7·5 mg. nicotinic acid) daily as soon as feeding was started. Vitamin C, 10 mg. on the first day of feeding, increasing (daily) by 10 mg. up to maximum of 100 mg. daily. Vitamin D, 50,000 I.U. ('calciferol'), was given at the age of 2 weeks and again at 1 month of age. At the age of 2 months (or before discharge if this occurred before the age of 2 months) 500,000 I.U. were given. Vitamin A, 15,000 I.U., was given daily from the age of 1 week. Calcium and phosphorus, syrup of calcium lactophosphate (7 minims per lb. of body weight daily ≡1 ml. per 1,100 g. body weight), was given from the fourteenth day. Iron, ferric ammonium citrate, 2½ grains (0·1,625 g.), was given once daily from the age of 1 month and this dose was gradually increased to 5 grains daily (2½ grains twice daily).

Change of Diet. When the diet to be given at home was different from that given in the Unit the change-over began in all cases when the baby reached the weight of 4½ lb. (2,042 g.) and was completed in about seven or eight days.

Clinical Observations during Stay in Hospital

Time Taken to Return to Birth Weight. Because babies in each weight group had a comparable period of initial starvation and were then given the same dilutions of the various diets, the average number of days taken to regain the birth weight by the babies in each weight group could be compared for the different diets (Table 3).

WEIGHT GROUPS 3-3½ LB. (1,361-1,588 g.) AND 3½-4 LB. (1,588-1,814 G.). In these groups the time taken to regain the birth weight was much the same in all diet groups. Babies fed on half-skimmed dried milk (diet C) and evaporated milk with added protein (diet E) took a slightly shorter time and babies on evaporated milk (diet B) and human milk with added protein (diet D) a slightly longer time than those fed on human milk.

WEIGHT GROUP 2½-3 LB. (1,134-1,361 g.). In this group unfortunately there were very few babies, but the worst results were obtained when protein was added to human milk (diet D) and to evaporated milk (diet E). This was probably due to intolerance of the added casein hydrolysate. One baby weighing 1 lb. 12 oz. (795 g.) at birth who was originally included in group D vomited persistently each time casein hydrolysate was added but did well on human milk alone and had to be excluded from the trials because of this change of diet. In the weight group 2-2½ lb. (907-1,134 g.) the three babies on half-skimmed dried milk (diet C) appeared to do better than the four babies fed on human milk, but not so well as the 1 lb. 14 oz. (852 g.) baby also fed on human milk. Babies fed on evaporated milk (diet B) regained their birth weights in about the same time as those on human milk. Evaporated milk (diet B) and half-skimmed dried milk (diet C) were both well tolerated.

Subsequent Gain in Weight. The time taken to regain the birth weight is obviously closely related to the

TABLE 3

AVERAGE NUMBER OF DAYS TAKEN TO REGAIN BIRTH WEIGHT

Birth Weight	A. Human Milk		B. Low-protein Cow's Milk Mixture (Evaporated Milk)		C. High-protein Cow's Milk Mixture (Dried Half-skimmed Milk)		D. Human Milk with added Protein		E. Low-protein Cow's Milk Mixture with Added Protein	
	Average Birth Weight	No. of Days	Average Birth Weight	No. of Days	Average Birth Weight	No. of Days	Average Birth Weight	No. Days	Average Birth Weight	No. of Days
up to 2 lb. (900 g.)	1 lb. 14 oz. (852 g.) (1 baby)	15·0	—	—	—	—	—	—	—	—
2 lb.–2½ lb. (900–1,140 g.)	2 lb. 5 oz. (1,049 g.) (4 babies)	17·75	2 lb. 6½ oz. (1,090 g.) (2 babies)	18·0	2 lb. 6½ oz. (1,090 g.) (3 babies)	15·6	2 lb. 3½ oz. (1,006 g.) (2 babies)	19·0	2 lb. 2½ oz. (979 g.) (2 babies)	21·0
2½ lb.–3 lb. (1,140–1,360 g.)	2 lb. 12½ oz. (1,260 g.)	15·6	2 lb. 12½ oz.) (1,255 g.)	20·0	2 lb. 13 oz. (1,276 g.)	14	2 lb. 14¾ oz. (1,325 g.)	22·3	2 lb. 12 oz. (1,248 g.)	14·2
Total up to 3 lb. (1,360 g.)	2 lb. 9½ oz. (1,180 g.)	16·1	2 lb. 11½ oz. (1,234 g.)	19·7	2 lb. 11 oz. (1,219 g.)	14·4	2 lb. 12 oz. (1,248 g.)	21·5	2 lb. 10 oz. (1,191 g.)	15·9
3 lb.–3½ lb. (1,360–1,590 g.)	3 lb. 4 oz. (1,474 g.)	14·75	3 lb. 5 oz. (1,503 g.)	16·7	3 lb. 4½ oz. (1,488 g.)	13·5	3 lb. 4 oz. (1,474 g.)	15·0	3 lb. 4 oz. (1,474 g.)	13·5
3½ lb.–4 lb. (1,590–1,820 g.)	3 lb. 13 oz. (1,730 g.)	12·0	3 lb. 12½ oz. (1,710 g.)	14·4	3 lb. 11 oz. (1,673 g.)	11·2	3 lb. 11 oz. (1,673 g.)	13·2	3 lb. 11½ oz. (1,687 g.)	12·0
Total over 3 lb. (1,360 g.)	3 lb. 7½ oz. (1,574 g.)	13·6	3 lb. 8½ oz. (1,602 g.)	15·6	3 lb. 7 oz. (1,560 g.)	12·9	3 lb. 8 oz. (1,588 g.)	14·5	3 lb. 8 oz. (1.588 g.)	12·9

condition of the baby at and shortly after birth. Weight gain must therefore also be examined at a later stage. Subsequent gain in weight is dependent to some degree on the actual weight and was therefore estimated by comparing the average time taken by babies in each birth weight group to increase their weights from the upper limit of their weight group to 4½ lb. (2,042 g.). (At this weight it was sometimes necessary to change the diet in preparation for discharge from hospital.)

Table 4 shows the average number of days taken to pass through each weight range under consideration for all weight groups up to 3½ lb. (1,588 g.). Babies weighing 3½-4 lb. (1,588-1,814 g.) had too short a period on their original diet to make it worth while comparing them in this way, but their progress is discussed later.

WEIGHT GROUP 3-3½ LB. (1,361-1,588 g.). Compared with babies fed on human milk, babies fed on half-skimmed milk (diet C) took a shorter time, and babies on evaporated milk with added protein (diet E) a longer time, while those on evaporated milk (diet B) and human milk with added protein (diet D) took approximately the same time. (One baby who died from infection was excluded from diet D.)

WEIGHT GROUP 2½-3 LB. (1,134-1,361 g.). Again babies on half-skimmed milk (diet C) took the shortest time. Those fed on evaporated milk (diet B) and human milk with added protein (diet D) were slowest (one baby with pneumonia was excluded from diet B). Evaporated milk with added protein (diet E) gave results comparable to human milk.

WEIGHT GROUP LESS THAN 2½ LB. (1,134 g.). It would appear that the best results were obtained with half-skimmed dried milk (diet C) and the worst with evaporated milk with added protein (diet E).

If one baby who died from infection had not been excluded from the group fed on human milk with added protein (diet D) the results on this diet would have been worse. This whole group is discussed more fully in relation to the weight curves.

Weight Gains Showed Graphically. To show the weight gains graphically the actual weights of each individual infant in each weight group were plotted, and from these graphs the average weight at any time of all cases in each diet group could be found. The average weight curves for each diet are shown in Fig. 1. The average birth weight of each diet group has been made to coincide with the same weight on an average foetal or *in utero* weight curve (Fig. 2, Crosse, 1952). The curves do not correspond exactly with the figures shown in Tables 3 and 4 because they are average curves; in addition the diet was changed as each individual baby reached a weight of 4½ lb. (2,042 g.) and not when the average curve reached this weight. The approximate age at which the change of food (if any) took place was as follows:

Weight Group	Age of Baby.
Under 2½ lb. (1,134 g.)	8–12 weeks
2½–3 lb. (1,134–1,361 g.)	7–10 ,,
3–3½ lb. (1,361–1,588 g.)	5–7 ,,
3½–4 lb. (1,588–1,814 g.)	4– 5 ,,

The average curves show in a general way the facts deduced from Tables 3 and 4.

WEIGHT GROUP 3½-4 LB. (1,588-1,814 g.). Once the birth weight had been regained, the average weight curves ran roughly parallel to the average weight curve of the foetus *in utero*, irrespective of the diet (Fig. 1A). But it should be remembered that the curves for babies fed on

TABLE 4

AVERAGE NUMBER OF DAYS TAKEN BY EACH WEIGHT GROUP TO REACH 4½ LB. FROM A STANDARD WEIGHT FOR EACH GROUP

Birth Weight	Weight Range Used	A. Breast Milk		B. Low-protein Cow's Milk Mixture (Evaporated Milk)		C. High-protein Cow's Milk Mixture (Half-dried Milk)		D. Breast Milk with Added Protein		E. Low-protein Cow's Milk Mixture with Added Protein	
		Average Birth Weight	Average No. of Days	Average Birth Weight	Average No. of Days	Average Birth Weight	Average No. of Days	Average Birth Weight	Average No. of Days	Average Birth Weight	Average No. of Days
2 lb.–2½ lb. (900–1,140 g.)	2½ lb.–4½ lb. (1,140–2,040 g.)	2 lb. 5 oz. (4 babies) (1,049 g.)	44·5	2 lb. 6½ oz. (2 babies) (1,090 g.)	43·75	2 lb. 6½ oz. (3 babies) (1,048 g.)	33·3	2 lb. 3½ oz. (2 babies) (1,006 g.)	37·5 1 infection death	2 lb. 2½ oz. (2 babies) (977 g.)	51·0
2½ lb.–3 lb. (1,140–1,360 g.)	3 lb.–4½ lb. (1,360–2,040 g.)	2 lb. 12½ oz. (10 babies) (1,262 g.)	30·3	2 lb. 12½ oz. (11 babies) (1,262 g.)	32·5 1 infection excluded	2 lb. 13 oz. (8 babies) (1,276 g.)	29·0	2 lb. 14¾ oz. (6 babies) (1,324 g.)	34·7	2 lb. 12½ oz. (6 babies) (1,262 g.)	30·5
3 lb.–3½ lb. 1,360–1,590 g.)	3½ lb.–4½ lb.) (1,590–2,040 g.)	3 lb. 4 oz. (12 babies) (1,474 g.)	17·0	3 lb. 5 oz. (10 (babies) (1,503 g.)	16·8	3 lb. 4½ oz. (14 babies) (1,488 g.)	15·0	3 lb. 4 oz. (12 babies) (1,474 g.)	16·8 1 infection death	3 lb. 4 oz. (11 babies) (1,474 g.)	19·0

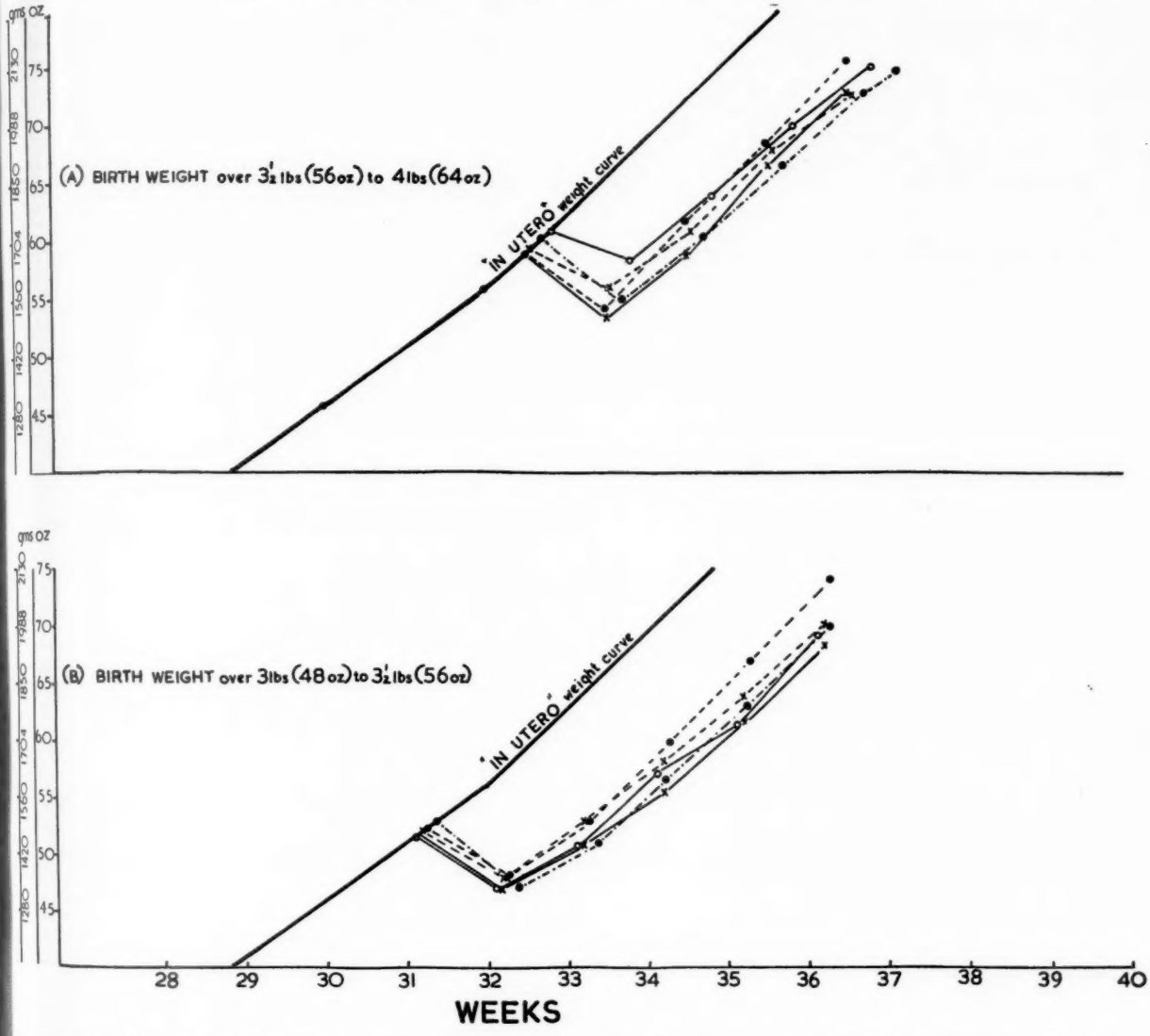
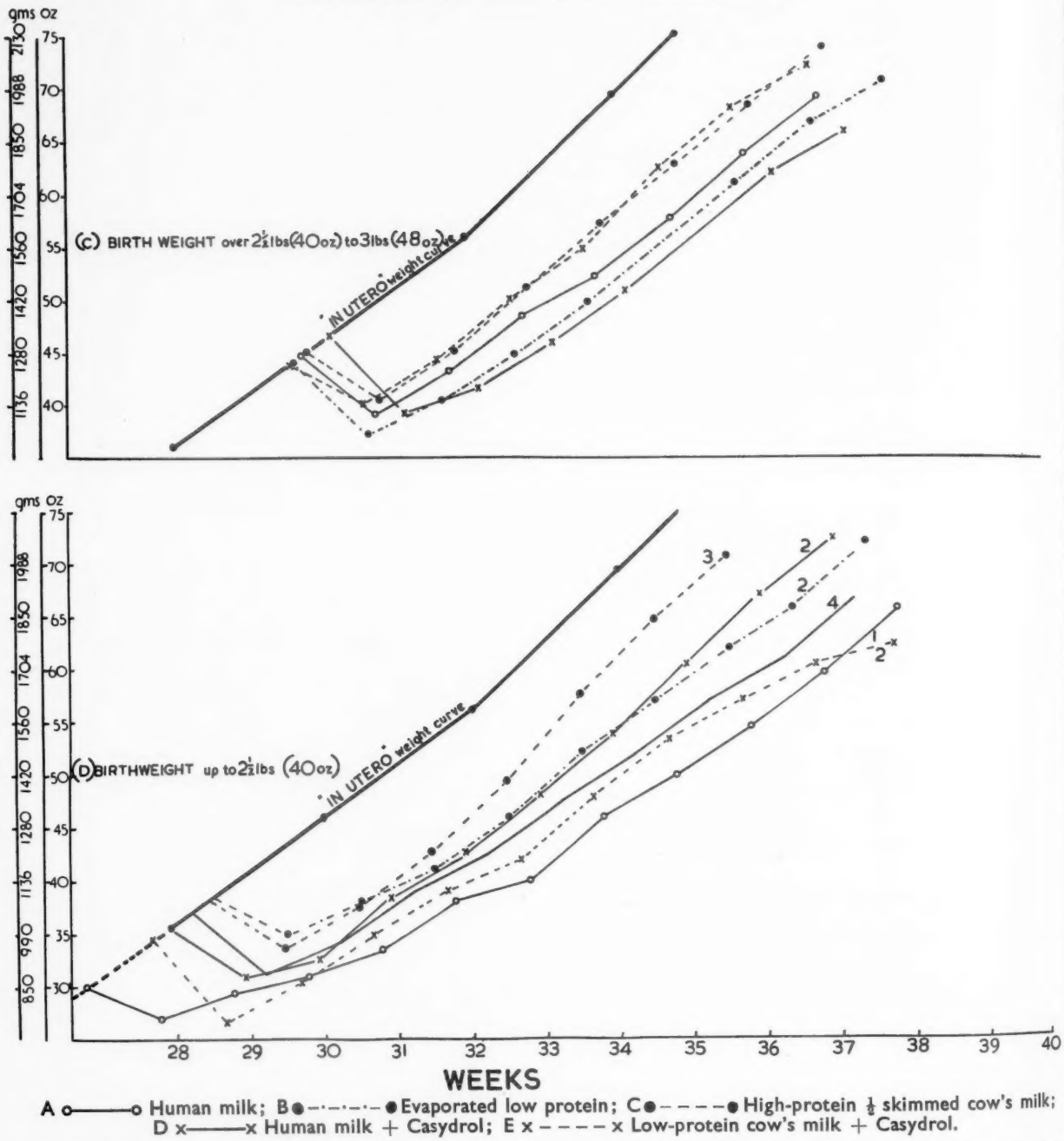

gms oz
(A) BIRTH WEIGHT over 3½ lbs (56 oz) to 4 lbs (64 oz)
'IN UTERO' weight curve
(B) BIRTH WEIGHT over 3 lbs (48 oz) to 3½ lbs (56 oz)
'IN UTERO' weight curve
28 29 30 31 32 33 34 35 36 37 38 39 40
WEEKS
A o——o Human milk; B ●–·–·–·–● Evaporated low protein; C ●– – – –● High-protein ½ skimmed cow's milk;
D x——x Human milk + Casydrol; E x – – – – x Low-protein cow's milk + Casydrol.

FIG. 1.—Average weight curves for each diet.

evaporated milk (diet B) and human milk with added protein (diet D) would not have been so good if one case which developed pneumonia had not been excluded from each (the case on human milk with added protein died). Some of the babies in this weight group were slightly oedematous during the first few days of life but whatever the diet very few developed any subsequent oedema unless they became anaemic.

WEIGHT GROUP 3-3½ LB. (1,361-1,588 g.). All average curves were approximately parallel to the *in utero* curve irrespective of the diet, but babies on half-skimmed dried milk (diet C) gained a little more rapidly than those on the other diets. One death from infection had been excluded from the group fed on human milk with added protein (diet D).

WEIGHT GROUP 2½-3 LB. (1,134-1,361 g.). The average curves still tended to run parallel to the *in utero* curve but at a slightly lower level, especially if the time taken to regain the birth weight had been prolonged. This finding seems to indicate the importance of using an easily digested and well tolerated diet during the first few weeks of life. After regaining the birth weight babies fed on half-skimmed dried milk (diet C) and evaporated milk with added protein (diet E) showed


gms oz
(C) BIRTH WEIGHT over 2½lbs(40oz) to 3lbs(48oz)
IN UTERO weight curve
(D) BIRTHWEIGHT up to 2½lbs (40oz)
IN UTERO weight curve
WEEKS

A o——o Human milk; B●-·-·-·-●Evaporated low protein; C●- - - -●High-protein ½ skimmed cow's milk;
D x——x Human milk + Casydrol; E x - - - - x Low-protein cow's milk + Casydrol.

slightly better curves and those on evaporated milk (diet B) and human milk with added protein (diet B) showed slightly worse curves than those fed on human milk. The curve for diet B would have been worse if a case of pneumonia had not been excluded because of the necessity to substitute human milk during the illness.

At this point it should be noted that the majority of babies in the two weight groups 2½-3 lb. (1,134-1,361 g.) and 3-3½ lb. (1,361-1,588 g.) showed early oedema which subsided rapidly, but among the group fed on half-skimmed dried milk (diet C) slight oedema usually developed again at the approximate age of 3 to 4 weeks (one or two weeks after reaching the full strength formula as set out in Table 2). The oedema was not usually obvious unless babies were carefully examined. It lasted for several weeks and must have accounted for at least part of the extra gain in weight among babies on this diet. This tendency for oedema to develop on half-skimmed cow's milk formula has already been reported by Hepner and Krause (1952). They

noticed that babies changed from human milk to this type of cow's milk diet developed thickening and hardening of the skin and in some cases frank pitting oedema of

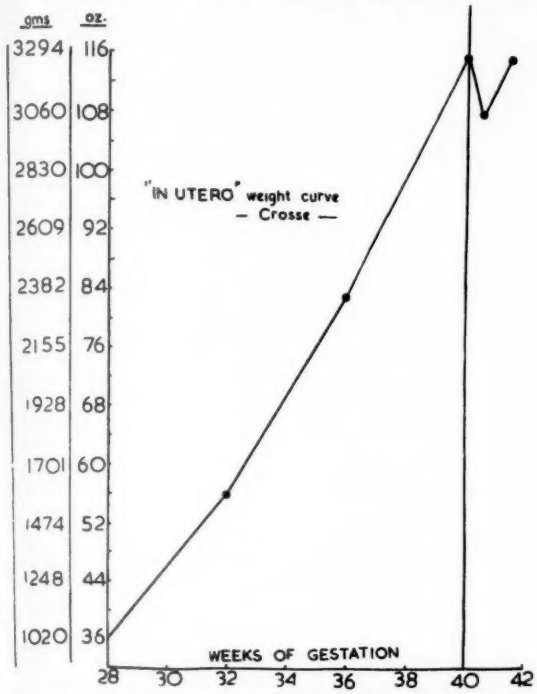


FIG. 2.—Average '*in utero*' weight curve (Crosse).

the scalp and ankles, and that a diuresis and a loss of weight occurred with disappearance of the oedema on a return to human milk, followed after a few days by a resumption of the original daily rate of gain. These workers also changed the diet of two babies aged 1 month from cow's milk to human milk and noted a temporary loss of weight accompanied by a decrease in the smoothness of the contours of the body and thinning of the skin. When these two babies were returned to their original cow's milk diet a sharp increase of weight occurred with thickening and increased firmness of the skin. These experiments have been repeated by one of us (V.M.C.) and we have found that all extra weight and oedema can be lost and regained by changing babies from half-skimmed dried milk (diet C) to human milk and vice versa. Gordon, Levine, Wheatley and Marples (1937) also observed excessive fluid retention with cow's milk formulae. Premature babies are known to have a limited capacity to excrete electrolytes (Young, Hallum and McCance, 1941), so this oedema was probably due to the inability of the immature kidneys of these smaller babies to cope with the high electrolyte content of half-skimmed dried milk.

WEIGHT GROUP UNDER 2½ LB. (1,134 g.). The babies in this group were too few to give significant average curves for each diet. Nevertheless curves have been plotted for what they are worth, with the number of babies in brackets against each curve. The three babies on half-skimmed dried milk (diet C) gave an average weight curve slightly better than the *in utero* curve but these babies all developed a slight degree of oedema which lasted for several weeks, and their gain was partially due to excessive water retention. The curve for babies on half-skimmed dried milk (diet C) was closely followed by that for two babies on human milk with added protein (diet D), but the baby who persistently vomited on diet D, and another baby who died of infection had been excluded. The two babies on evaporated milk with added protein (diet E) gave the worst curve. One baby weighing 1 lb. 14 oz. (852 g.) at birth (curve shown separately in Fig. 1D) did well on human milk: so did a baby weighing 1 lb. 12 oz. (795 g.) at birth who could not tolerate human milk with added protein (diet D) but the latter could not be included in the reports of this investigation because of the change of diet.

Even if large numbers of these small babies were available for trial, it would still be difficult to assess the value of different diets, because their survival and progress depend so much more on such factors as development of the lungs, the presence or absence of birth injury, and other complications.

The following points emerged from a study of the rate of gain while the infants were in hospital.

(1) In all weight-groups, babies fed on half-skimmed dried milk (diet C) made the most rapid progress, both in regaining the birth weight and in the subsequent rate of gain. This diet was well tolerated, even by the smaller babies.

(2) Evaporated milk was well tolerated, but generally speaking babies fed on this diet gained the least rapidly.

(3) The addition of casein hydrolysate to human milk and to evaporated milk (diet B) was not well tolerated by babies under 2½ lb. (1,134 g.) at birth during early life. Later this addition was well tolerated but made no striking difference to the rate of gain.

(4) The difference between the rate of gain among babies fed on half-skimmed dried milk (diet C) and on human milk was at least partially due to the difference in the hydration of the babies in the two groups, babies on human milk retaining less water than those on diet C.

(5) In the light of these trials, there is no doubt in the minds of the nursing and medical staff at Sorrento that human milk is the diet which is best tolerated by the very small infants (under 2½ lb. (1,134 g.) at birth) during the first few weeks of life. It also appears to be the best diet for any premature baby whose tolerance to food has been reduced by infection.

Anaemia and Transfusions. The degree of anaemia developed by premature babies on different diets is

TABLE 5
BABIES REQUIRING TRANSFUSION

Birth Weight	A. Human Milk		B. Low-protein Cow's Milk (Evaporated Milk)		C. High-protein Cow's Milk Mixture (Half Skimmed Dried Milk)		D. Human Milk with Added Protein		E. Low-protein Cow's Milk Mixture with Added Protein	
	Babies in Group	Babies Transfused	Babies in Group	Babies Transfused	Babies in Group	Babies Transfused	Babies in Group	Babies Transfused	Babies in Group	Babies Transfused
2 lb.–2½ lb. (900–1,140 g.)	4	2	2	2	3	2	2	—	2	2
2½ lb–3 lb. (1,140–1,360 g.)	10	6	11	11	8	4	6	5	6	2
Total 2 lb.–3 lb. (900–1,360 g.)	14	8=57%	13	13=100%	11	6=54%	8	5=63%	8	4=50%
3 lb.–3½ lb. (1,360–1,600 g.)	12	2	10	3	14	4	12	1	11	3
3½ lb.–4 lb. (1,600–1,810 g.)	8	1	10	2	9	1	4	—	7	—
Total 3 lb.–4 lb. (1,360–1,810 g.)	20	3=15%	20	5=25%	23	5=22%	16	1=6%	18	3=17%
Grand Total	34	11=32%	33	18=55%	34	11=32%	24	6=25%	26	7=27%

another way of assessing the value of the diets. Weekly haemoglobin estimations were made on all babies on the same colorimeter, and the time of introduction of iron into the diet was the same for all babies. Indications for transfusion were: (1) a haemoglobin level of less than 9·0 g. at any time during the first 10 weeks of life; (2) a haemoglobin level less than 10 g. and rapidly falling, in a baby under 10 weeks of age who was due for discharge from hospital.

Babies were transfused with packed cells (10 ml. per lb. body weight) by the scalp vein route, and the number of those who required this treatment is shown in Table 5. In all weight groups, babies fed on evaporated milk (diet B) required the highest proportion of transfusions. There was little difference between the proportion of babies transfused among the three high-protein diet groups (diets C, D, and E) or between them and the group fed on human milk.

Judging by haemoglobin levels it would appear that evaporated milk (diet B) was not a good food for premature babies.

Incidence of Infection during Stay in Premature Baby Unit. Every infection which occurred among the babies under review was recorded, however mild; and these infections have been divided into two classes.

(1) Minor: Sticky eyes; Mild skin infections; Thrush; Moist cord (no definite infection); Paronychia; Slight nasal discharge

(2) Major: Otitis media; Lung infections; Loose stools; Urinary infections; Deep abscess; Cord infection

Table 6 shows the proportion of infected babies in each diet and weight group. Babies with more than one infection were included among those with major infections if one of their infections belonged to this class.

In order to obtain the true proportions of infected babies in each group it was necessary to include five babies, who were excluded from the rest of the investigation, i.e., three who died of infection during the trials (all fed on human milk with added protein, diet D,) and two who became so ill with pneumonia that it was necessary to change their diet to human milk (both were originally on evaporated milk, diet B.)

TABLE 6
PERCENTAGE IN EACH GROUP INFECTED DURING STAY IN PREMATURE BABY UNIT

	A. Human Milk		B. Low-protein Cow's Milk Mixture (Evaporated Milk)		C. High-protein Cow's Milk Mixture (Half-skimmed Milk)		D. Human Milk with Added Protein		E. Low-protein Cow's Milk Mixture with Added Protein	
Birth Weight	Minor	Major	Minor	Major	Minor	Major	Minor	Major	Minor	Major
2 lb.–3 lb. (900–1,360 g.)	43	36	21	50	18	36	38	50 (1 death)	50	25
3 lb.–4 lb. (1,360–1,810 g.)	35	Nil	40	5	31	4	19	31 (2 deaths)	33	22

Because the numbers are small the babies have been considered in two groups, those under 3 lb. (1,361 g.) and those between 3 and 4 lb. (1,361 and 1,814 g.) and because the major infections are most likely to be affected by the diet the following remarks will refer to the proportions who developed major infections.

In the 2-3 lb. (937-1,361 g.) group, the highest proportions of infected babies were found among those fed on evaporated milk (diet B) and human milk with added protein (diet D) (one death on diet D) and the lowest on evaporated milk with added protein (diet E). Babies fed on human milk and half-skimmed dried milk (diet C) suffered equally from severe infections.

In the 3-4 lb. (1,361-1,814 g.) group the highest proportions of infected babies were among those fed on human milk with added protein (diet D; two babies on this diet died of infections) and on evaporated milk with added protein (diet E). The lowest proportions were found among those fed on human milk.

Considering all weight groups together, the least infection occurred among babies fed on human milk, followed closely by those fed on half-skimmed dried milk (diet C). The greatest amount of infection occurred among babies fed on human milk with added protein (diet D; three babies in this diet group died from infections). Babies fed on evaporated milk (diet B) and evaporated milk with added protein (diet E) had almost as high an infection rate as those fed on human milk with added protein (diet D).

Mortality during Stay in Premature Baby Unit. Babies who died after being allotted to a diet group are shown in their correct weight and diet group in Table 7. Neither of the deaths among babies fed on human milk could reasonably be related to the diet. The three deaths among babies fed on human milk with added protein (diet D) were all due to infection. There were no deaths among babies fed on the other three diets during their stay in hospital, although there were two serious cases of pneumonia among the groups fed on evaporated milk (diet B).

Follow-up of Regular Attenders to the Age of 6 Months

Babies included in this investigation were followed up at a special out-patients' clinic. Some could not attend the clinic because of the distance involved (up to 120 miles), and several failed to attend in spite of repeated invitations. The following results are limited to those babies seen regularly every month up to 6 months of age. At each attendance, weight, haemoglobin and infections were recorded and blood was taken for chemical examination. Advice on feeding was given.

Feeding after Discharge from Hospital. Few babies went home completely breast-fed. (This was before the addition of mothers' quarters to the Unit.) Of the 12 babies able to be breast fed, six had been on low-protein diets (three on human milk and three on evaporated milk, diet B), and six on high-protein diets (one on half-skimmed dried milk, diet C, three on human milk with added protein, diet D, and two on evaporated milk with added protein, diet E). For the purpose of the follow-up these babies were grouped together irrespective of their diet while in hospital. All babies unable to be breast-fed after discharge were changed to the diet they would have at home when they

TABLE 7

MORTALITY DURING STAY IN PREMATURE BABY UNIT

Birth Weight	A. Human Milk	B. Low-protein Cow's Milk (Evaporated Milk)	C. High-protein Cow's Milk Mixture (Half-skimmed dried Milk)	D. Human Milk with Added Protein	E. Low-protein Cow's Milk Mixture with Added Protein
Up to 2 lb. (900 g.) ..	—	—	—	—	—
2–2½ lb. (900–1,130 g.)	—	—	—	1 death at 6 weeks (*Bact. coli* meningitis)	—
2½–3 lb.(1,130–1,360 g.)	* 1 died at 16 days (strangulated hernia) * 1 died at 17 days (atelectasis only)	—	—	—	—
3–3½ lb. (1,360–1,590 g.)	—	—	—	1 death at 17 days (pneumonia)	—
3½–4 lb. (1,590–1,820 g.)	—	—	—	1 death at 35 days (? pneumonia no P.M.)	—

* Deaths not attributable to method of feeding.

TABLE 8
SIX MONTHS FOLLOW-UP OF REGULAR ATTENDERS

Diet from Weight of 4½ lb. (2,040 g.)	I. Breast-fed	II. New Low-protein Cow's Milk (Full-cream Dried Milk)	III. New High-protein Cow's Milk Mixture (Half-skimmed Dried Milk)		
Diet until weight of 4½ lb. (2,040 g.)	3 Diet A 3 ,, B 1 ,, C 3 ,, D 2 ,, E	Low-protein Cow's Milk Mixture (Diet B)	High-protein Cow's Milk Mixture (33 Diet C) (24 Diet E)	Breast Milk (Diet A)	Breast Milk with added Protein (Diet D)
No. originally in each new group	12	30	57	32	21
No. followed regularly in clinic until 6 months	10=83%	17=57%	38=67%	25=78%	15=71%
Average birth weight of those followed	3 lb. 6 oz. (1,531 g.)	3 lb. 3½ oz. (1,460 g.)	3 lb. 2¼ oz. (1,426 g.)	3 lb. 1½ oz. (1,403 g.)	3 lb. 2¾ oz. (1,440 g.)
Average weight at 6 months of those followed	14 lb. 3½ oz. (6,455 g.)	12 lb. 10 oz. (5,732 g.)	13 lb. 4 oz. (5,916 g.)	13 lb. 2 oz. (5,859 g.)	13 lb. 9½ oz. (6,072 g.)
Average haemoglobin level at 6 months of those followed	11·7 g.	10·9 g.	10·0 g.	11·4 g.	11·2 g.
Major infections after discharge in those followed	Nil	2 chickenpox 1 diarrhoea } 3	4 diarrhoea 2 whooping cough } 6	1 Chickenpox 2 otitis media 2 bronchitis 2 diarrhoea } 7	Bronchitis 1
Deaths among babies followed	Nil	Nil	2 whooping cough 2 unknown cause 1 diarrhoea	Nil	Nil

reached a weight of 4½ lb. (2,042 g.). Those previously fed on evaporated milk (diet B) were changed to another relatively low-protein cow's milk mixture, i.e., 1 in 12 full-cream dried milk mixture with 1 drachm (4 g.) of sugar to every 2 oz. (56 ml.) of the mixture (protein 2·2%, fat 2·2%, sugar 9·2%, calories 20 per oz.). The remaining babies who had been fed on the high-protein diets (33 on diet C, 21 on diet D, and 24 on diet E) and the remaining 32 babies who had been fed previously on human milk were given a new high-protein cow's milk mixture, i.e., half-skimmed dried milk 1 in 8 with 1 drachm (4 g.) of sugar to every 3 oz. (85 ml.) of the mixture (protein 3·8%, fat 2·1%, sugar 9·5%, calories 21 per oz.). Apart from the groups originally fed on human milk, those who had been on the low-protein diet continued on another low-protein diet while those who had been on the three high-protein diets continued on another high-protein diet. This will be seen in Table 8.

Clinical Observations at 6 Months of Age. Table 8 sets out the findings at the age of 6 months.

WEIGHT. Babies who were breast fed after discharge from hospital had a heavier average weight than any other group, even taking into account their slightly greater average birth weight. Of the remaining groups babies always fed on a low-protein cow's milk mixture did rather worse than all others.

HAEMOGLOBIN LEVELS. Babies who had had some breast milk, either in the Unit or after discharge, had a higher average level of haemoglobin than babies always fed on cow's milk.

MAJOR INFECTIONS. There had been no infection among the 12 breast-fed babies but three out of 30 of those fed on the low-protein cow's milk mixture and seven out of 32 of those fed on the high-protein cow's milk mixture had suffered from major infections.

DEATHS. The only deaths had occurred among the group always fed on high-protein diets (before and after discharge). In two cases the cause was unknown but the other three were all due to infections. There were no deaths among the 12 breast-fed babies, whereas five out of 110 infants fed on cow's milk had died. The breast-fed group was very small and these figures could not be considered significant. But in this connexion one of us (Crosse, 1952) has already shown the much greater risk of mortality from the age of 1 to 6 months among premature babies fed on cow's milk than among those fed on human milk.

Rickets. Some of the babies in those feeding trials were included in a rickets investigation which covered 227 infants. The wrists were radiographed at the age of 3 months. Minimal signs of rickets were found in 15 of the 109 babies fed entirely on

human milk and in 30 out of 118 babies fed entirely on cow's milk. No infant showed clinical signs of rickets and all radiographs were normal by the age of 6 months. All children had been given the supplements already described.

Retrolental Fibroplasia. Five babies included in these feeding trials developed retrolental fibroplasia. All had received oxygen for periods varying from 18 to 30 days. One of these babies had originally been fed on human milk, one on human milk with added protein (diet D) and two on evaporated milk with added protein (diet E). The fundi were normal in all cases until two or three weeks after changing to half-skimmed dried milk (diet C), and oedema had occurred in all these cases at the time that the first signs appeared.

Follow-up to Age of 1 Year

As only about two-thirds of the babies under investigation had been followed up regularly until the age of 6 months, it was felt that all of them should be traced at the age of 1 year to discover the final mortality rate in each group. This was done from the '1-year-old report' cards returned by the parents, and for those who failed to return the card, through the local health authority concerned.

Table 9 shows that there were still no deaths among the 12 infants sent home completely breast fed, whereas 10 out of the total 140 infants fed on cow's milk had died before the age of 1 year.

Observations on the Serum Protein Levels

Blood specimens were taken from a scalp vein if possible at weekly intervals. Total protein was estimated using a micro-Kjeldahl digestion with H_2SO_4-$CuSO_4$ mixture, adding selenium oxide after partial digestion, followed by steam distillation (Broadbent and Finch, 1950). Correction was made for the non-protein-nitrogen values determined on the same specimens. Albumin was estimated by the same method on the filtrate after precipitating globulin with 22·2% sodium sulphate at 38°C.

The values of the serum proteins (total, albumin and globulin) for the first 12 weeks of life for each child were plotted separately. They showed the same wide scatter as was found by Young *et al.* (1950) working in the same laboratory and are not shown in this report. The averages of the curves for each weight group on the various diets are shown in Fig. 3 together with the levels as determined on normal full-term infants (Poyner-Wall and Finch, 1950).

The babies over 2½ lb. (1,134 g.) birth weight will be considered first (Fig. 3, A.B.C.).

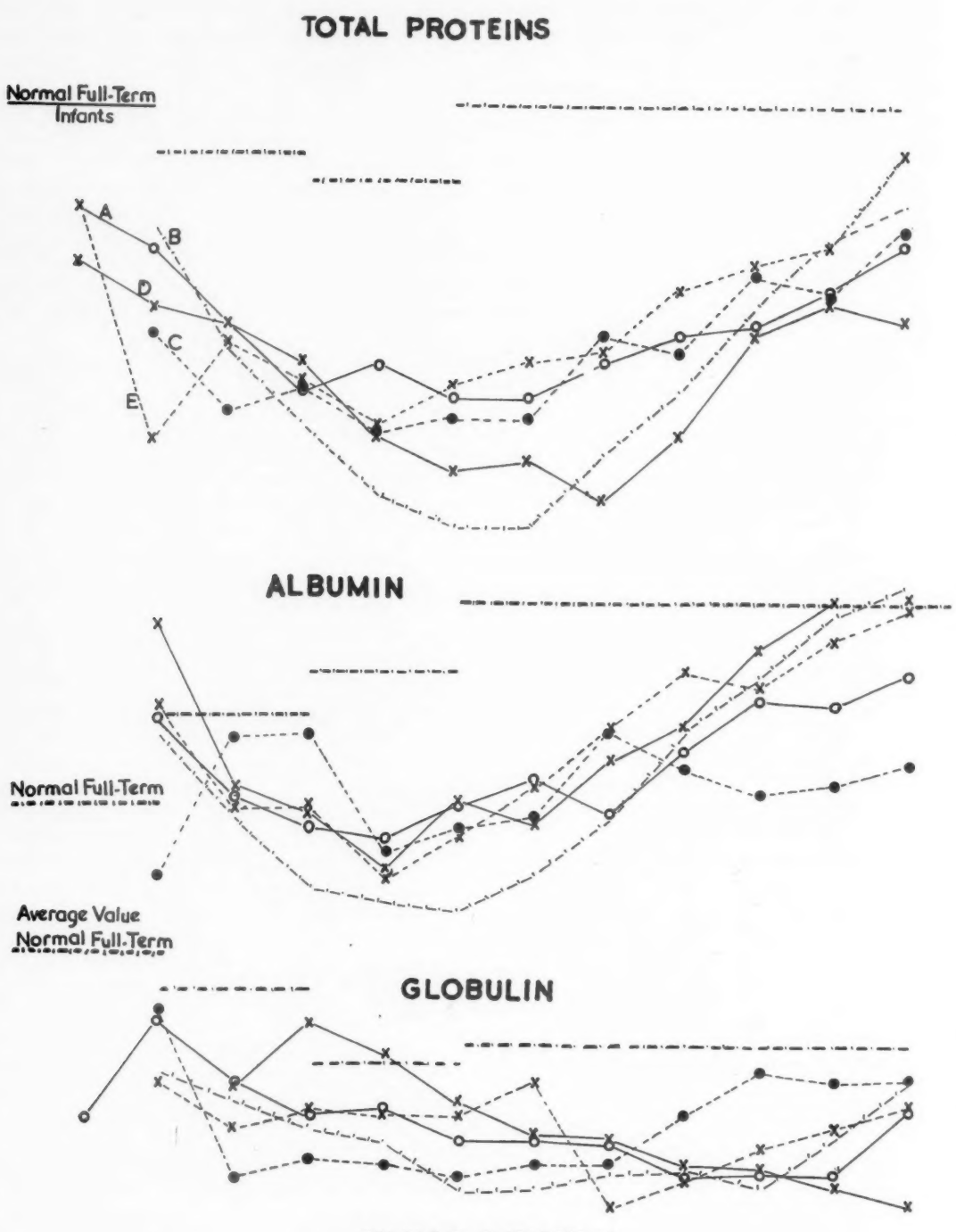
Total Proteins. The average curves show that the smaller and less mature the babies, the lower were the levels of serum total protein during the first week of life and for approximately the first three months of life, being well below the average levels for normal full-term infants. This may be related to the immaturity of the liver where many fractions of the serum proteins are formed, among them albumin and globulin. The total protein levels fell for some six or eight weeks, the fall being greater and more prolonged in the smaller babies than in the bigger babies, whatever food was given. This fall is more or less parallel with the fall of total protein levels shown by normal full-term infants, but at a lower level. It may possibly be explained as a normal physiological process. In the babies with a birth-weight over 3½ lb. (1,588 g.) the level of that of full-term normal children was attained at about 10 weeks of age, but this level was not reached by the babies with a birth weight of less than 3½ lb. (1,588 g.) in the 12 weeks of observation owing probably to the lower levels at birth.

The kind of food given seems to have made no

TABLE 9

FOLLOW-UP FROM DISCHARGE UNTIL AGE OF 1 YEAR (152 BABIES)

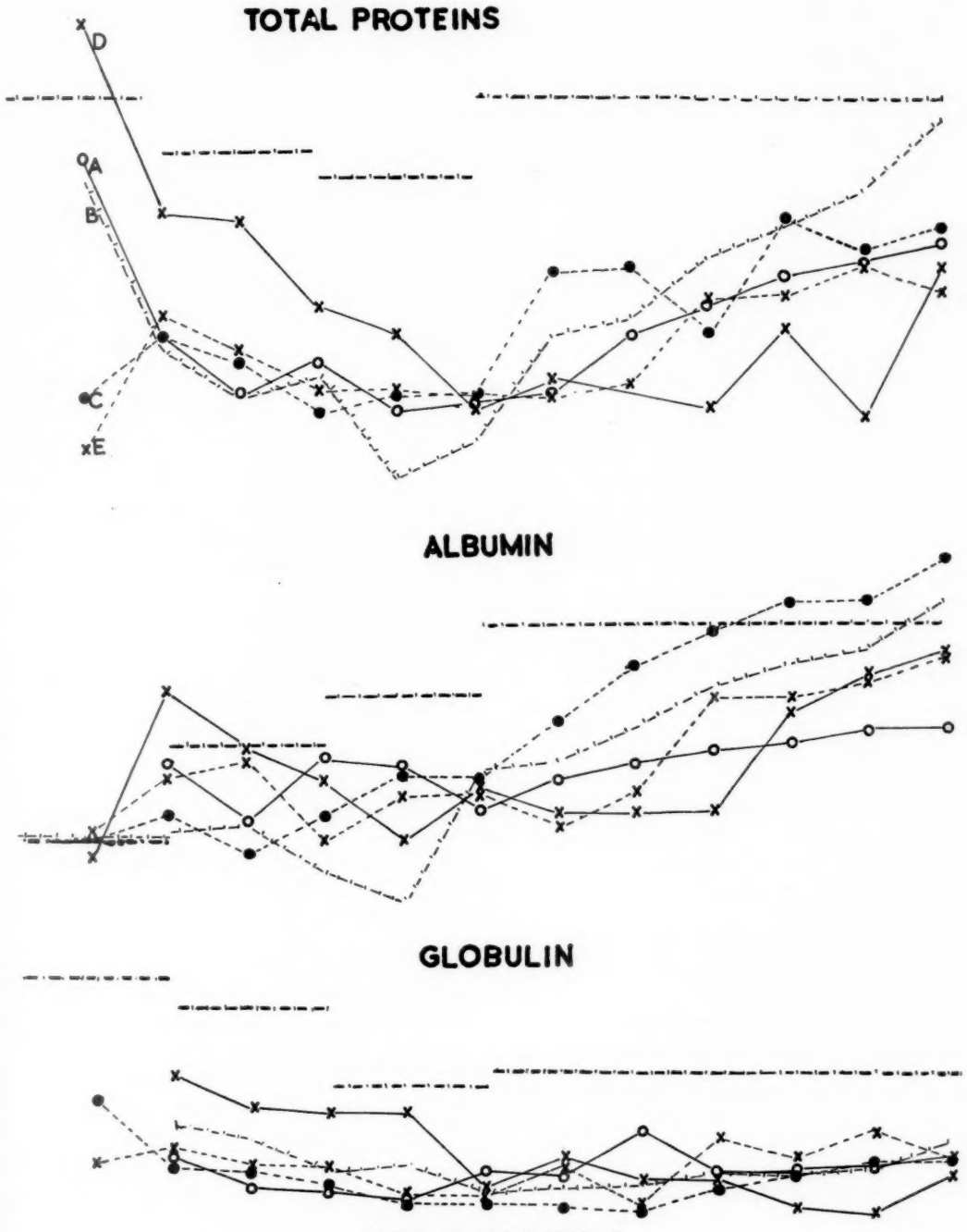
Diet from 4½ lb.	I. Breast Fed	II. New Low-protein Cow's Milk Mixture (Full-cream Dried)	III. New High-protein Cow's Milk Mixture (Half-skimmed dried)		
Diet until 4½ lb. (2,042 g.) ..	3 Diet A 3 „ B 1 „ C 3 „ D 2 „ E	Diet B	33 diet C 24 diet E	Diet A	Diet D
No. originally in each new diet group	12	30	57	32	21
No. dead at one year ..	None	1	7	2	None
Causes of death ..	—	Unknown 1	Whooping cough 2 Diarrhoea 3 Unknown 2	Diarrhoea 1 Unknown 1	—



(A) 2½-3 lb. (1,134-1,361 g.)

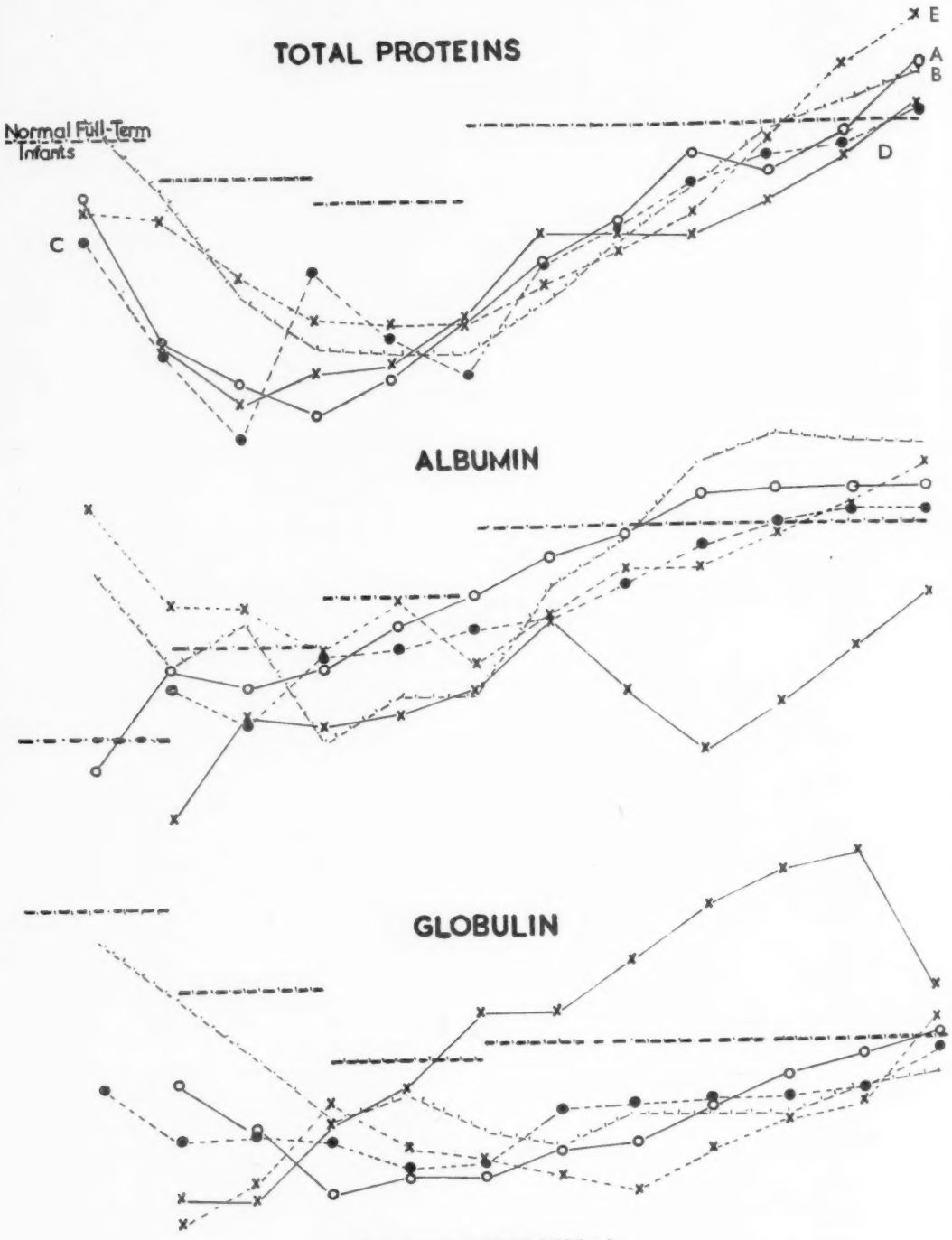
o———o Human milk; B–|–|–|–Evaporated low protein; C ●– – – – ● High-protein ½ skimmed cow's milk; D x———x Human milk + Casydrol; E x – – – – x Low-protein cow's milk + Casydrol.

FIG. 3.—Values for serum protein levels for each birth-weight group.



(B) 3-3½ lb. (1,361-1,581 g.)

FIG. 3.



(C) 3½-4 lb. (1,588-1,814 g.)

A o——o Human milk; B –·–·– Evaporated low protein; C ●– – – –● High-protein ½ skimmed cow's milk; D x——x Human milk + Casydrol; E x – – – – x Low-protein cow's milk + Casydrol.

FIG. 3.

consistent differences in the results in babies over 3 lb. (1,361 g.) birth weight. In the babies with birth weight 2½-3 lb. (1,134-1,361 g.) the evaporated milk (diet B) and human milk with added protein (diet D) showed the worst results, viz., a very low total protein and such foods should probably be considered unsuitable for very small infants. There was apparently little difference between the other three diets. It must be borne in mind, however, that when the babies reached a weight of 4½ lb. (2,042 g.) the food was sometimes changed as indicated earlier in this paper, but it is interesting to note that before the change was made the protein levels had already started to rise. The very low total protein levels reached by the group with birth weight to 2½-3 lb. (1,134-1,361 g.) may have been due to protein insufficient in amount for very small premature children in the case of those fed on evaporated milk (diet B), or of unsuitable quality when protein was added to human milk (diet D).

In relation to the blood serum protein levels it would appear that human milk provides sufficient protein for the needs of the premature baby since the curves for the babies fed on human milk maintained a consistently good level throughout the 12 weeks of observation.

Albumin. The levels of the total proteins are obviously related to the levels of the albumin rather than the globulin, for the total protein curves and the albumin curves showed somewhat similar falls and rises. It is interesting to note that while the albumin in normal full-term infants rises continually from birth, there was a definite fall in the albumin level of the premature babies under observation particularly amongst the group with birth weight of 2½ to 3 lb. (1,134-1,361 g.) but in spite of this all groups made good progress between eight and 12 weeks and by this time had reached the levels found for normal full-term infants of the same age. Again the type of food seems to make little difference to the final results except in the case of the smallest babies fed on low-protein cow's milk whose serum albumin reached the lowest levels recorded.

Globulin. The level of globulin at birth was low compared with normal full-term infants, particularly during the first two weeks, and maintained rather a low level steadily throughout the period of observation, being little affected by the diet. The continuous subnormal level may account to some extent for the increased susceptibility of the premature baby to infection.

Results in Infants with Birth Weight under 2½ lb. (1,134 g.). Although it was not possible to obtain blood very regularly, especially in the early weeks of life, such results as were obtained on 13 babies with birth weight between 2 and 2½ lb. (907-1,134 g.) and one baby with a birth weight of 1 lb. 14 oz. (852 g.) were graphed on a large scale. The curves were very erratic and confused and are not reproduced here. There is little doubt that the erratic levels were partially due to small transfusions which were frequently given to those tiny babies in the early days of life. However, it became clear that on the whole there was not a great difference between the actual levels of total protein on any of the diets, though they all reached considerably lower levels at about 6 weeks of age than the group of babies with birth weight of 2½ to 3 lb. (1,134-1,361 g.) and remained at a lower level for more than 12 weeks. The albumin levels and globulin also fell to much lower levels than those in the 2½-3 lb. (1,134-1,361 g.) weight group. The lowest curves were shown by the one baby on low-protein evaporated cow's milk and one on breast milk with added casein hydrolysate and this is probably another indication that these are undesirable foods for very small premature infants.

Summary

Clinical and biochemical observations have been made on 152 babies weighing less than 4 lb. at birth to determine which of five selected diets gave the best result judged by the rate of gain in weight, serum protein and haemoglobin levels, infection and mortality rates. These babies were also examined for the presence of rickets and for retrolental fibroplasia.

Babies fed on human milk have been compared with babies fed on (*a*) human milk reinforced with hydrolysed casein, (*b*) a low-protein cow's milk mixture (diluted evaporated milk), (*c*) a cow's milk mixture with a high-protein content (half-skimmed dried milk) and a high-protein cow's milk mixture in which part of the protein was hydrolysed (diluted evaporated milk reinforced with hydrolysed casein). The fat content of all three cow's milk mixtures was the same and all five diets had equal caloric values.

Weight. The quickest return to birth weight was achieved by babies fed on the half-skimmed dried milk. Those fed on human milk did almost as well (and indeed human milk was often the only food well tolerated by infants under 2 lb. (907 g.) at birth), while those fed on the low-protein evaporated cow's milk mixture did not do so well. The addition of casein hydrolysate was badly tolerated by infants

weighing less than 2½ lb. (1,134 g.) at birth. Over this weight, the added protein appeared to reduce the time taken by babies fed on the low-protein evaporated cow's milk mixture but the time was not reduced when hydrolysed protein was added to human milk.

The rate of subsequent gain in hospital was very similar in all babies weighing more than 3½ lb. (1,588 g.) at birth, irrespective of diet. Below this birth weight the most rapid progress was made by babies fed on half-skimmed dried milk but it is likely that this was largely due to excessive water retention, because the majority of these babies developed slight pitting oedema. Human milk gave almost as good results except in the small group weighing less than 2½ lb. (1,134 g.) at birth. The least rapid gains were found among babies fed on the low-protein evaporated cow's milk mixture. Generally speaking, the addition of hydrolysed casein to human milk and to the low-protein evaporated cow's milk mixture did not improve the rate of gain.

After discharge from hospital breast-fed babies gained more rapidly than those fed on cow's milk. Babies fed on a low-protein cow's milk mixture gained the least rapidly.

Anaemia. During their stay in hospital the highest proportion of babies requiring transfusion was among those fed on the low-protein cow's milk diet. The proportions requiring transfusion were similar among babies fed on human milk and the three high-protein diets.

Incidence of Infection. Babies fed on human milk had the lowest incidence of major infections while in hospital, followed closely by babies fed on the half-skimmed dried milk. Babies fed on the low-protein evaporated cow's milk mixture had the highest infection rate during this period. After discharge and until the age of 6 months, there were no major infections among the 12 breast fed infants, but three out of 30 of those fed on the low-protein evaporated cow's milk mixture and seven out of 32 of those fed on the half-skimmed dried milk had developed such infections.

Mortality. During their stay in hospital three babies who were fed on the low-protein evaporated cow's milk mixture died of infection. After discharge, there were 10 deaths before the age of 1 year among the 140 babies fed on cows' milk mixtures, while there were no deaths among the 12 breast-fed infants. These figures are obviously not statistically significant, but one of us (Crosse, 1952) has shown similar results for large numbers of babies.

Rickets. A parallel investigation, which included some of the babies in this study, indicated that babies on human milk showed less tendency to develop rickets than babies fed on cow's milk, when they were given adequate supplements of vitamins, calcium and phosphorus.

Retrolental Fibroplasia. Five babies in this investigation developed retrolental fibroplasia. One had been fed on human milk, two on the low-protein evaporated cow's milk mixture and two on human milk with added casein hydrolysate but there were no signs of abnormality until two or three weeks after the diets had been changed to undiluted half-skimmed cow's milk (half-skimmed dried milk 1 in 8). The first signs of abnormality usually coincided with the development of oedema. All five babies had received oxygen for periods varying from 18 to 30 days, these trials having been carried out before the relevance of oxygen had been recognized.

Serum Protein Levels. Total protein levels were always below the normal level for full-term infants during the first 12 weeks of life except in the case of babies with birth weights of 3½ to 4 lb. (1,588 g.-1,814 g.) who reached normal levels between 10 and 12 weeks. Among babies with birth weights of over 3 lb. (1,361 g.) diet made little difference but under this weight the curves for babies fed on the low-protein evaporated cow's milk mixture and on human milk with added casein hydrolysate reached the lowest levels.

The albumin levels fell for a few weeks after birth instead of rising as in the full-term infant. Normal levels were reached at about the age of 8 weeks among babies over 3½ lb. (1,588 g.) but not until 12 weeks or more among those weighing less than 3½ lb. (1,588 g.). The lowest levels were found among the smallest babies fed on the low-protein evaporated cow's milk mixture. There was little difference between the curves for other diets.

The globulin levels were nearly all below the levels for full-term babies, especially during the first two weeks of life, and tended to maintain a constant level. Diet appeared to make little difference.

Conclusions

We cannot subscribe to the opinion of those who state that human milk is unsuitable or inferior for premature babies. It is the food which is best tolerated by the smallest babies during the first few weeks of life and by sick premature babies. The return to the birth weight is not prolonged and the

subsequent weight curves run parallel to the *in utero* curve if sufficient calories are given (60 per lb. (450 g.) daily). There is no evidence to show that anaemia or hypoproteinaemia are more common among infants fed on human milk than on high-protein diets. The incidence of infection and mortality are lowest among those fed on this natural food. Provided adequate vitamin and mineral salt supplements are given, the incidence of rickets is lower among infants fed on human milk than among those fed on cow's milk. It is also possible (Hepner and Krause, 1952) that babies fed entirely on human milk are less liable to develop retrolental fibroplasia.

There is no doubt that the half-skimmed dried milk mixture produces a more rapid gain in weight during the first six to eight weeks of life, but there is good reason to believe that this is mainly due to increased water retention and not true growth. If human milk cannot be obtained, half-skimmed dried milk is a fairly good substitute. This diet gives similar results to those obtained with human milk in regard to haemoglobin and serum protein levels; the hospital infection rate among babies fed in this way was similar to that among babies fed on human milk but after discharge from hospital seven of the 32 babies fed on half-skimmed milk developed major infections while the 12 breast-fed babies remained free from infection. There may be an increased risk of retrolental fibroplasia due to the high electrolytic content.

We have found ample evidence to support the suggestion of Young *et al.* (1950) that cow's milk with a protein content similar to human milk might not be a good food for premature babies. Babies fed on the low-protein evaporated cow's milk diet showed the slowest return to birth weight and the least rapid subsequent rate of gain, the highest proportion of babies requiring transfusion, the lowest serum protein levels and the highest hospital infection rate. The low-protein evaporated cow's milk mixture did not appear to supply sufficient protein of the correct quality to meet the needs of a premature baby. The addition of casein hydrolysate to the low-protein cow's milk mixture tended to minimize the disadvantages of this diet, but was not always well tolerated by small infants during the early days of life.

Contrary to the findings of Jorpes *et al.* (1946) the addition of casein hydrolysate to human milk gave worse results than unfortified human milk in relation to time taken to regain the birth weight (this was due to intolerance of the added protein by some of the smaller babies), serum protein levels, incidence of hospital infection and mortality rate.

In our opinion, human milk is the best food for premature babies. In the absence of an adequate supply of human milk, it would appear that the best substitute is a cow's milk mixture with a protein content considerably higher than that found in human milk, and that there is no need for this protein to be hydrolysed. There would however appear to be a case for the use of a half-skimmed milk with a lower electrolyte content in view of the excessive hydration of babies on this food and the possibility of an increased liability to develop retrolental fibroplasia due to this cause. There is plenty of evidence to suggest that a cow's milk mixture with a low-protein content should not be used for premature babies.

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SOME OBSERVATIONS ON THE CLOSURE OF THE ANTERIOR FONTANELLE

BY

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Early observers (Elsässer, 1843; Friedleben, 1860; Roger, 1859) have claimed that the dimensions of the anterior fontanelle of the human skull increase from the time of birth until about the age of 9 months, and that it is, as a rule, closed at the age of 18 months. Scammon (1923), reviewing this literature, challenged these observations on the grounds that the material studied involved European children of the poorer classes, many of them born prematurely, and many suffering from rickets. He argued that the observations did not necessarily apply to the 'better nourished and more rapidly growing American children', but he did not publish any figures of his own to substantiate his views. Zahorsky (1944) published observations on the date of closure of the anterior fontanelle in American children. Since his subjects were all seen in private practice they probably do not represent an accurate cross-section of the population. He estimated closure of the fontanelle by palpation and tried to correlate the time when it occurred with the type of feed the infants had received in the first four months of life. Aisenson (1950) examined 1,677 New York children in his health clinic and estimated that the mean age of closure of the anterior fontanelle was 13·5 months.

Material

The children on whom the observations presented in this paper were made were those in the Oxford Child Health Survey. Of the 580 children who attended in the first year (Stewart and Russell, 1952) there were 530 (270 boys and 260 girls) with records of fontanelle closure.

Each child was examined clinically at the age of 3 months, and thereafter at three-monthly-intervals during the first year; subsequently the child was seen every six months until the age of 5. From the age of 6 months radiographic examinations were made at half-yearly intervals; 127 children (59 boys and 68 girls) had a lateral radiograph of the skull taken at each half-yearly visit.

Results

Fontanelle Closure Assessed Radiologically and Clinically. In the group of children who had radiographs taken of the skull, the age at which the anterior fontanelle ceased to be apparent was noted. From the clinical records of the same children the age of closure as judged by palpation was obtained. A comparison of the clinical and radiographic methods has been made (Table 1). The variation

TABLE 1

FONTANELLE CLOSURE ASSESSED CLINICALLY AND RADIOLOGICALLY

Age in Years	Boys		Girls	
	Clinical	Radiological	Clinical	Radiological
	% closed	% closed	% closed	% closed
½	1·7 (59)	3·6 (56)	0 (69)	0 (56)
1	30·5 (58)	29·6 (54)	18·8 (64)	21·0 (62)
1½	90·6 (53)	75·5 (49)	70·3 (64)	69·8 (63)
2	98·1 (53)	95·8 (48)	96·9 (64)	92·7 (68)
2½	98·1 (53)	97·9 (48)	98·4 (64)	97·0 (68)
3	100 (53)	100 (49)	98·4 (64)	98·5 (68)
3½	100 (53)	100 (49)	98·4 (64)	98·5 (68)
4	100 (53)	100 (49)	98·4 (64)	98·5 (68)
4½	100 (53)	100 (49)	100 (64)	98·5 (68)
5	100 (53)	100 (49)	100 (64)	100 (68)

Figures in brackets indicate the number of observations.

in the total number of children examined from one age group to the next is either due to the fact that certain children did not present themselves for examination, or to incompleteness of the records. According to the figures in the table more boys

than girls had, at given ages, closed fontanelles. The precocity of the boys in this respect is also shown by the mean ages at closure of the fontanelle as judged by clinical methods and radiographs, viz. Table 2. The age of closure of the fontanelle is

TABLE 2
MEAN AGE OF FONTANELLE CLOSURE

Sex	Judged Radiologically	Judged Clinically
Boys	17·9	16·3
Girls	19·7	18·8

understandably earlier when judged clinically, but the difference is slight. It will be seen that mean age of closure is later for Oxford children than was reported by Aisenson for New York children (1950).

Fontanelle Closure and Skeletal Maturity. Since the differences in radiological and clinical estimates were small, there seemed to be no contra-indication to using the clinical method of assessment for further studies. Thus it was possible to increase the size of the sample studied to include the whole survey group. For these larger numbers no significant correlation was found between the state of the fontanelle and the maturity of the hand and wrist at 1 year. This was true when skeletal maturity was estimated both by the method of Todd (1937) and by that of Acheson (1954).

Fontanelle Closure and the Deciduous Dentition. No correlation was found between fontanelle closure and the number of deciduous teeth which had erupted at any age.

Fontanelle Closure and Height. An attempt was made to correlate the standing height with the age of closure of the fontanelle. Values for height were not available until age 1½ years. At this age 43% of the boys and 38% of the girls were able to stand still long enough for their height to be measured. In order to determine whether 'early' closure occurred in tall or short children, height at 1½ years was correlated with the state of the fontanelle at 1 year. The correlation for girls between tallness and early fontanelle closure was significant at the 0·25% level. No significant correlation could be found between these two variables for the boys for these ages. In order to exclude the possibility that the relatively small number of children of each sex whose standing height was recorded at 1½ years could have influenced the result, the standing height at 2 years was compared with the fontanelle at 1 and 2 years. Again a significant correlation was found for the girls (this time at the 3% level) and not for the boys.

Fontanelle Closure and Skull Circumference. No significant correlation between skull growth, as reflected by maximum circumference, and fontanelle closure was found in either sex. This is in accordance with the observation of Ehrlich (1927).

Fontanelle Closure and Social Class. Consideration of the effect of environment on the age at which the fontanelle closed gave some unlooked-for results. The children were divided into social classes (Registrar General, 1951) (Tables 3 and 4). It will be seen that there is a tendency for

TABLE 3
CLOSURE OF FONTANELLE AND SOCIAL CLASS
(BOYS)

Age at Examination (Months)	Percentage Boys with Closed Fontanelle			
	All Classes	Social Classes I and II	Social Class III	Social Classes IV and V
6	0·7	0·0	1·1	0·0
9	7·0	7·9	6·4	8·9
12	28·1	15·8	27·3	42·2
18	74·1	71·1	74·9	73·3
24	95·9	94·7	96·3	95·6
30	98·9	100·0	98·9	97·8
36	100·0	100·0	100·0	100·0
No. of boys	270	38	187	45

TABLE 4.
CLOSURE OF FONTANELLE AND SOCIAL CLASS
(GIRLS)

Age at Examination (Months)	Percentage Girls with Closed Fontanelle			
	All Classes	Social Classes I and II	Social Class III	Social Classes IV and V
6	0·4	0·0	0·6	0·0
9	6·2	4·3	5·8	8·5
12	25·8	21·4	27·5	23·4
18	72·3	66·7	71·3	80·9
24	91·5	90·5	91·2	93·6
30	98·5	100·0	97·7	100·0
36	99·6*	100·0	99·4*	100·0
No. of girls	260	42	171	47

* In one girl closure occurred between the ages of 48 and 54 months.

children of Social Classes IV and V to close the fontanelles before those of Social Classes I and II. The class difference is significant at the 5% level for boys aged 1 year but the differences observed in the girls are not significant. It is reported elsewhere (Acheson and Hewitt, 1954) that Oxford boys of Social Classes I and II are taller, and skeletally more mature (Todd) than those of Social Classes IV and V, but the girls show little difference in respect of stature and none in respect of skeletal maturity.

Discussion

The closure of the fontanelle must be largely dependent on the growth of the bones bordering on it. This investigation suggests that the development of the membrane bones in the skull is geared differently from that of bones preformed in cartilage. Since it is generally accepted that skeletal maturation in the female occurs more rapidly than in the male (Pryor, 1905, etc.) the earlier closure of the anterior fontanelle in the male is a particularly interesting observation and one which so far as we know had not been noted previously.

The fact that tallness is correlated with early fontanelle closure in girls and not in boys may be a reflection of the fact that the male is more easily upset by an adverse environment than the female (Greulich, 1951; Greulich, Crismon and Turner, 1953; Acheson and Hewitt, 1954). In other words, a fundamental relationship between early fontanelle closure and tallness may have been masked in the male by his greater susceptibility to environmental factors.

The later fontanelle closure in the higher social classes cannot be explained in the light of the present data.

Summary

The age of closure of the anterior fontanelle has been studied clinically in 530 children of both sexes, and radiographically in 127 of these children.

In this sample the anterior fontanelle closed earlier in the male than in the female. This distinguishes fontanelle closure from skeletal maturation in which the female lead is well known.

Significant statistical correlations have been found between an early fontanelle closure and (*a*) above-average height in the female, (*b*) adverse social circumstances in the male.

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PULMONARY HYALINE MEMBRANES IN THE NEWBORN

BY

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In some infants dying within the first week of life, microscopical studies of the lung tissue show homogeneous, hyaline membranes lining the alveolar ducts and proximal alveoli. A common associated finding is atelectasis of the peripheral lung tissue. The hyaline membranes are seen more frequently in premature than in full-term infants, and only in infants who have breathed.

Infants with hyaline membranes in most instances present a typical sequelae of clinical events. During the first few hours after birth there may be no pathological physical findings. Later in the course of the first day, however, cyanosis appears. At the same time the infant's respirations are heavy and frequent and apparently ineffective as they fail to improve the colour. In our experience, a diminution in the intensity of the breath sounds has been a frequent observation. A marked disproportion between the exaggerated respirations and the diminished breath sounds may thus be an outstanding feature.

This syndrome has recently attracted great attention and has often been discussed in the current paediatric literature (Ahvenainen, 1948; Blystad, Landing and Smith, 1951; Marstrander, 1953; Miller, 1951). Several theories of the pathogenesis of this syndrome have been advanced, but a definite cause has not been demonstrated.

Material

The following analysis comprises 56 cases of hyaline membranes, detected in 216 consecutive necropsies. These were all infants who died during the first week of life, and were examined at The Institute of Pathological Anatomy, University of Oslo, during the six-year period from 1948 to 1953. In every case the microscopical slides, usually two slides from each lung, were re-examined by us.

Fig. 1 shows the distribution of all cases of hyaline membranes in relation to birth weight and age at death. It may be seen that 70% of these infants died within the first 24 hours of life. Further, 70% of all the infants with hyaline membranes were premature.

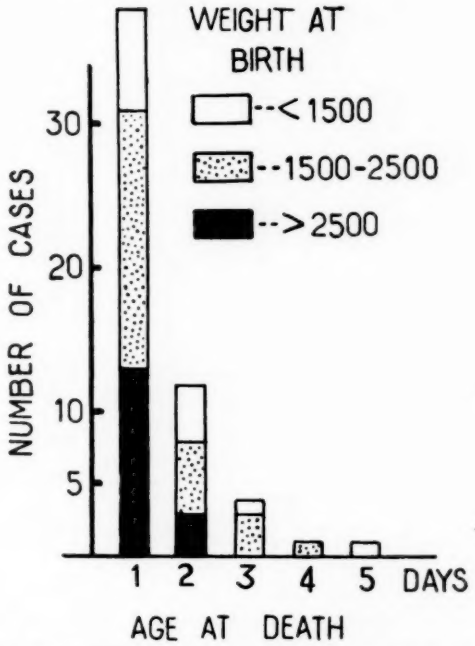

FIG. 1.—The distribution in relation to birth weight (in. g.) and age at death of 56 cases of pulmonary hyaline membranes.

Fig. 2 shows all premature infants who died within the first week of life, and the proportion with hyaline membranes (black columns). It will be seen that roughly half of the premature infants who died within the first three days had hyaline membranes in the lungs.

At necropsy, 23 of the 56 infants with hyaline membranes presented other pathological conditions considered capable of explaining death. These were pneumonia, malformations, erythroblastosis, or intracranial haemorrhage, all of severe grade, with a distribution as shown in Fig. 3, and were found (1) in 10 of 38 infants who died within the first 24 hours of life (26%); (2) in 13 of 18 infants who died during the second to fifth day of life (72%).

Slight intracranial or pulmonary haemorrhage is considered asphyxial, and has therefore not been included.

Discussion

The frequency and distribution of hyaline membranes, as shown in Figs. 1 and 2, accord with observations reported by other authors. Arey (1949), Blystad *et al.* (1951) and Potter (1952) thus found it more frequently in premature than in full-term infants. Potter (1952) found hyaline-like membranes as the only pathological change in 40% of all infants weighing from 1,000 to 2,500 g. in a 10-year period. Blystad *et al.* (1951) found hyaline membranes in roughly half of all premature infants studied.

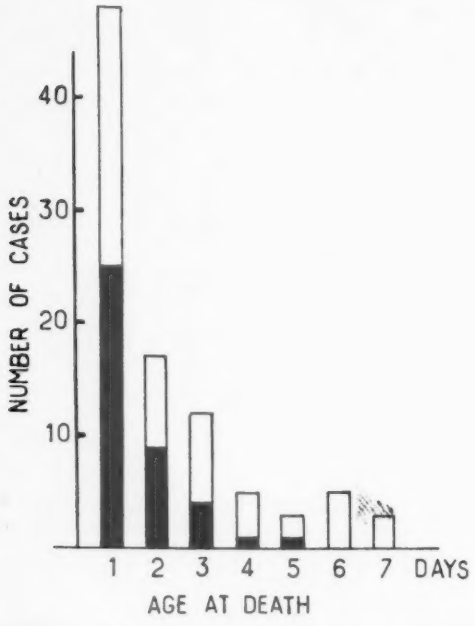

FIG. 2.—Cases of hyaline membranes (black columns) among all premature infants who died within the first week of life.

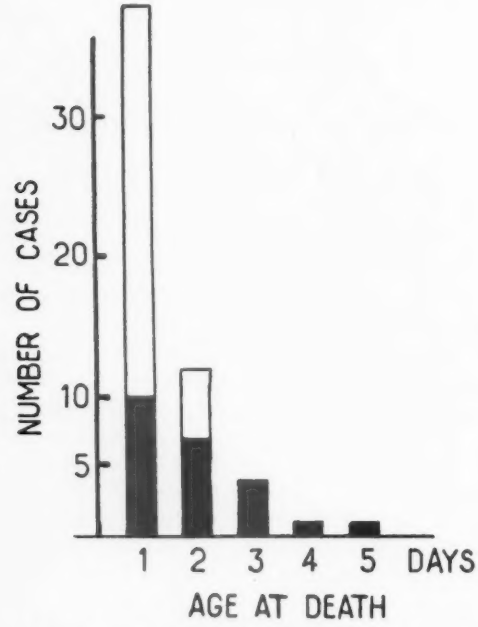

FIG. 3.—Other major pathological conditions (black columns) in infants with hyaline membranes.

As to the actual cause of death in cases of hyaline membranes, Potter (1953) states that the respiratory difficulty frequently causes death within 24 hours, and she claims that 'in infants surviving more than 48 hours after birth, we have never found an uncomplicated hyaline membrane'.

This is in good accordance with our findings. Our series, although small, indicates that the first day of life is especially critical in infants with hyaline membranes. Twenty-eight infants who died within the first day presented no other major pathological condition, while only five infants who died after the first day showed uncomplicated hyaline membranes at necropsy. In 10 infants dying within the first day, and in 13 dying within the next four days, death might have been due to other causes than hyaline membranes. Even in these cases, however, hyaline membranes must at least be considered a contributory cause.

Clifford (1953) states that the vast majority of infants with hyaline membranes may recover on or about the fourth day of the disease. Our observations indicate that in suspected cases of hyaline membranes, therapeutic measures should be instituted even in the first hours of life, in order to minimize the risk of a fatal outcome.

Summary

An analysis is given of 56 infants with pulmonary hyaline membranes examined post mortem. The findings indicate that the first day of life is especially critical in infants presenting this syndrome. Most infants with hyaline membranes who died after the first day of life presented severe accompanying lesions at necropsy.

Before death, a marked disproportion between the exaggerated respiratory movements and the diminished breath sounds was found to be an outstanding feature.

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THE SURVIVAL OF TRANSFUSED RED CELLS IN ACUTE RHEUMATIC FEVER WITH REFERENCE TO A LATENT HAEMOLYTIC MECHANISM

BY

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Acute rheumatic fever is commonly associated with anaemia, and the degree of this anaemia and rapidity of its onset is proportionate to the severity of the disease. Osler (1892) described it as being the most severe of any anaemia associated with infection. Dyshaemopoiesis (Hubbard and McKee, 1939) and an increase in plasma volume (Cochran, 1951) have both been put forward as causes, and, although it has been suggested that haemolysis plays a part (Hubbard and McKee, 1939), there has hitherto been no satisfactory evidence for this hypothesis.

In the course of observing patients with acute rheumatic fever, the rapidity of the onset of anaemia has been most striking. This has given rise to the present investigation to detect whether a haemolytic process is operative in the acute stage of the disease.

Evidence of haemolysis has been sought in a study of the survival of transfused normal red cells in the circulation of patients with acute rheumatic fever using the Ashby technique. Previous personal observations on the osmotic and mechanical fragility of the red cells, the serial reticulocyte count and the serum bilirubin and faecal urobilinogen output have indicated that if haemolysis is present, it is not of marked degree. However, latent haemolytic mechanisms, where the process may only be revealed by special studies such as the survival of transfused red cells, are known to occur in a variety of conditions, and particularly with acute infections (Brown, Hayward, Powell and Witts, 1944; Emerson, 1948; Berlin, 1951; Loge, Lange and Moore, 1950).

The survival of transfused red cells in the circulation of normal recipients and of those with various diseases has been investigated to estimate the mean red cell life. Ashby (1919) introduced a method of differential agglutination using the ABO blood groups to count the donor cell population and she made estimations of the normal red cell life in certain haemolytic conditions. The Ashby technique was subject to too many inaccuracies in its original form for it to come into common use as a method of studying haemolysis. The modifications of Mollison and Young (1940), and of Dacie and Mollison (1943) have done much to improve its accuracy in recent years. The normal mean cell life of 100 to 120 days, determined by this method, correlates well with that found by estimating the survival of the subject's own cells in his circulation by tagging them with N_{15} labelled glycine (Shemin and Rittenberg, 1946). The Ashby technique with its recent modifications is now widely accepted as a useful method for studying haemolytic mechanisms (Brown *et al.*, 1944; Berlin, 1951; Mollison, 1947; Young and Lawrence, 1946).

Method

The survival of transfused red cells was estimated by Dacie and Mollison's (1943) modification of the Ashby technique. In the author's hands, the coefficient of variation of this method was found to be 3·3%.

Material

The material included in this study was composed of eight cases of acute rheumatic fever. In addition six control cases were studied comprising cases of hypochromic anaemia, anaemia following haemorrhage and normal convalescent cases. In all of these conditions, normal survival of transfused red cells has been shown previously (Mollison, 1947; Callender, Powell and Witts, 1945; Kaplan and Zuelzer, 1950).

Control Series

It is known that the elimination of transfused normal red cells in the circulation of normal recipients occurs at a steady rate, 0·83% of the total introduced at transfusion being destroyed each day (Callender *et al.*, 1945). Thus the slope of elimination is linear (Mollison, 1947) and the average total

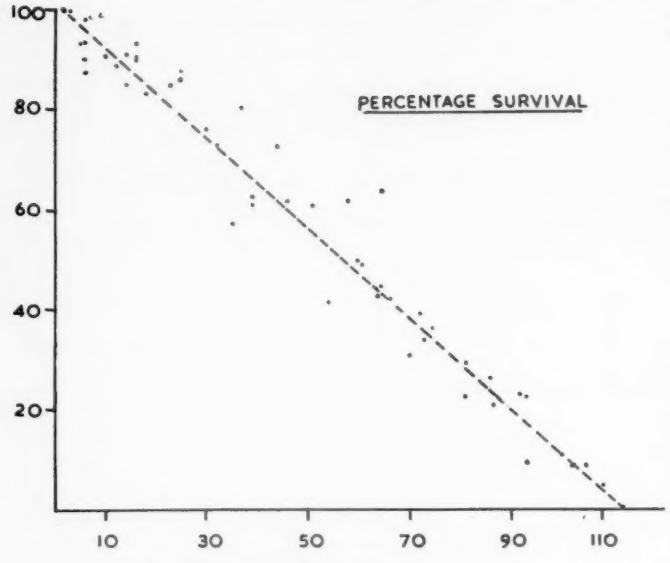

FIG. 1.—Survival of transfused red cells in six control cases.

survival time has been variously estimated at between 100 and 120 days.

In Fig. 1 points indicating percentage survival in the six control cases are plotted on one graph. A straight line has been fitted to these points by inspection and this gives an estimate of the normal elimination of donor red cells by the methods used in this investigation. It will be seen that the mean cell life is about 116 days.

Cases of Acute Rheumatic Fever

Eight cases were transfused in the acute stage of the disease and one was again transfused when the disease was considered to be inactive. She suffered a relapse of the condition 22 days after the second transfusion, and following this the transfused red cells were eliminated more rapidly than normal.

In all cases of rheumatic fever during the acute phase of the illness the elimination of transfused red cells was more rapid than normal and the slope was curvilinear. This indicates that the cells were being destroyed in a random manner irrespective of the normal process of ageing. This is demonstrated in Fig. 2, and is related to the normal slope of elimination derived from the control series. In three cases, undergoing an acute relapse in the course of elimination of donor cells from their circulation, the rate of elimination was further increased.

Analysis of Material

The results in acute rheumatic fever are compared below with the normal findings in the six cases in this control series and with the normal controls in the series of Mollison (1947) and of Callender *et al.* (1945) in adults, and that of Kaplan and Zuelzer (1950) in children.

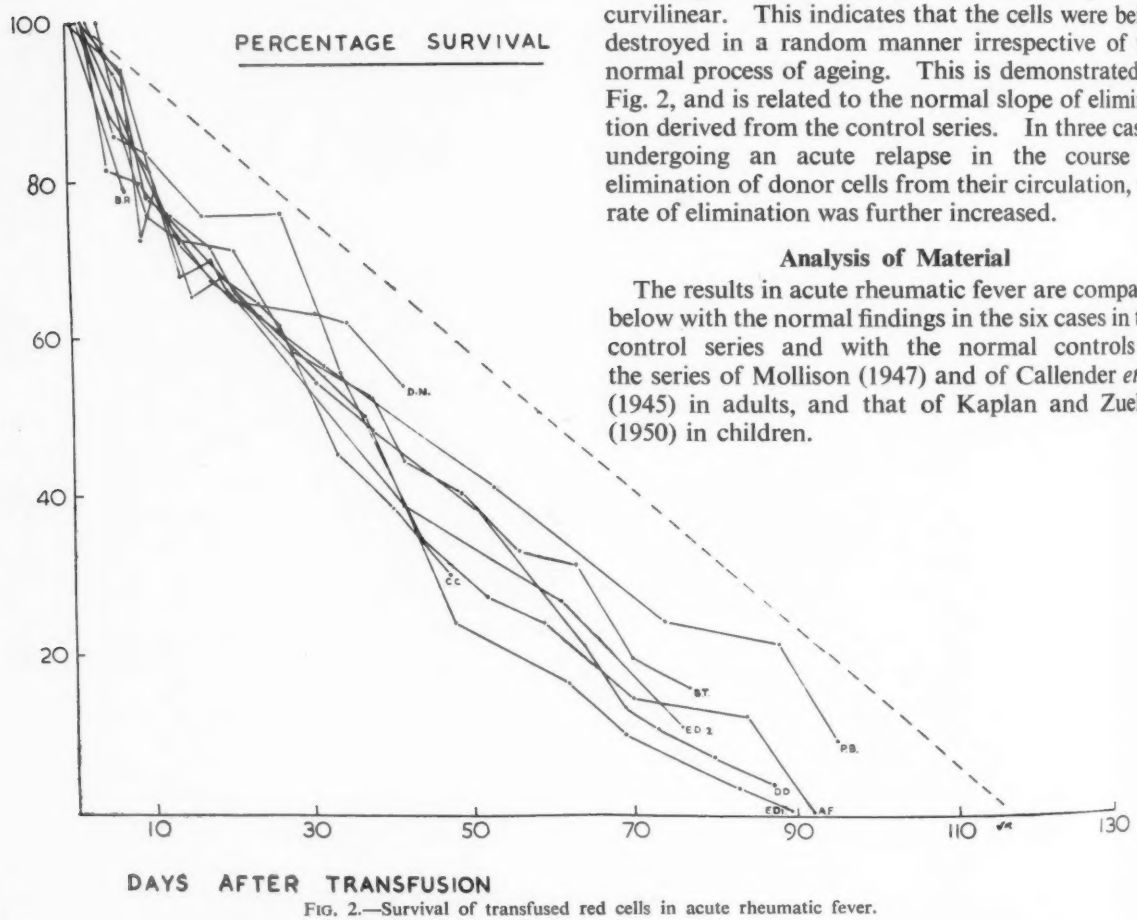

FIG. 2.—Survival of transfused red cells in acute rheumatic fever.

Where transfused red cells are being destroyed in a random manner irrespective of their age, an estimate of mean cell survival becomes an inexact method of expressing results. Some workers have preferred the half-life of the donor cells as a way of expressing results (Young and Lawrence, 1946), while others estimate the time after transfusion at which 50% survival occurs (Berlin, 1951). In expressing results in these cases of acute rheumatic fever, where the greatest activity of the disease occurred in the first 20 to 30 days after transfusion, the percentage survival at 10 and 20 days after transfusion seems most likely to give the maximum information.

Mollison's Normal Series. The percentage survival of transfused red cells has been estimated at 10 and 20 days after transfusion in 11 of the control cases from this series. They consisted of cases of hypochromic anaemia, convalescent cases and of one healthy subject.

Case No.	Percentage Survival at 10 Days	Percentage Survival at 20 Days
1	85	73·5
2	88	72·5
3	91	76·5
4	91	83·5
5	94	82·5
6	95·5	85
7	95·5	86·6
8	96·0	87·5
9	97·0	91·0
10	97·5	95
11	99·0	87
Mean	93·6 (σ=4·33)	83·7 (σ=7·06)

Callender *et al.* (1945), in an investigation into the life-span of the red cell, concluded that the normal mode of destruction of erythrocytes acts so as to remove in unit time a fixed fraction of the total introduced at transfusion. They estimated this fraction at 0·83% per day. On this assumption, survival 10 days after transfusion would be 92·7% and 20 days after transfusion would be 83·4%.

Kaplan and Zuelzer's Normal Series in Children. These investigators studied the survival of normal transfused red cells in the circulation of five "normal" infants and children. Their "normal" controls consisted of children in hospital convalescent from various medical or surgical illnesses and free of any haematological abnormality save for iron deficiency anaemia in some cases. The mean survival at 10 and 20 days after transfusion in this series has also been calculated.

Case No.	Percentage Survival at 10 Days	Percentage Survival at 20 Days
1	81	73
2	88	88
3	96	94
4	96	81
5	99	88
Mean	92 (σ=7·4)	85 (σ=8·1)

Control Cases in the Present series. These findings for percentage survival 10 and 20 days after transfusion compare very closely with those in the other control studies described above.

Case No.	A Percentage Survival at 10 days	B Percentage Survival at 20 days
1	95·2	81·5
2	90·7	81·5
3	89	82
4	97	90
5	90	87·5
6	97	88
Mean	93·2 (σ=3·66)	85·1 (σ=3·84)

Percentage Survival at 10 and 20 Days in Acute Rheumatic Fever. This has been estimated in eight cases 10 days after transfusion and in seven cases 20 days after transfusion. In view of the relatively small number of cases in the control and rheumatic fever series, Student's t test was applied to the results to estimate the significance of the differences observed. Comparing the mean percentage survival at 10 days after transfusion in the control series (A) and in the rheumatic fever series (A1), t=8·17. Therefore the differences observed would occur by chance less than once in a thousand times. Similarly comparing survival at 20 days after transfusion (B and B1), t=8·34, and therefore the observed differences would again occur by chance less than once in a thousand times. From this it can be stated that these results are statistically highly significant.

Case	A1 Percentage Survival at 10 Days	B1 Percentage Survival at 20 Days
E.D. (1)	83·5	67·5
C.C. ..	82	67·5
A.F. ..	81	75·5
P.B. (1) ..	78·5	67·2
D.D. ..	78·0	68·5
B.T. ..	76·0	70
D.N. ..	76·0	66
B.R. ..	79·0 (at 7 days)	—
Mean	79·3 (σ=2·73)	68·9 (σ=3·16)

Discussion

The survival of transfused red cells has been extensively studied in the various forms of haemolytic

anaemia and these investigations have done much towards clarifying the aetiology of these conditions. For instance, fundamental abnormality of the erythron in familial haemolytic anaemia has been demonstrated by showing that, whereas blood from normal donors survives normally in the circulation of these patients, their red cells have a greatly diminished survival rate in normal recipients (Loutit and Mollison, 1946).

In idiopathic acquired haemolytic anaemia, normal donor red cells are very rapidly destroyed, in extreme cases only 50% surviving after three to five days (Loutit and Mollison, 1946). This abnormal destruction of donor cells may occur either in a linear fashion (Mollison, 1947) or by means of a curvilinear slope of elimination indicating random destruction of cells irrespective of their age (Brown *et al.*, 1944); the latter appears to be by far the more common finding in such cases. Such results have been reported by many authorities (Young and Lawrence, 1946; Mollison, 1947; Selwyn and Hackett, 1949; Brown, 1950), and the value of transfused red cell survival experiments in the evaluation of haemolytic mechanisms is now generally recognized.

Acquired haemolytic anaemias associated with other diseases have been grouped together under the title of the symptomatic haemolytic anaemias. Haemolysis in these conditions is often easily demonstrated. In some instances evidence of haemolysis may be less obvious, and in an increasing number of diseases the presence of a latent haemolytic mechanism is being detected by transfused red cell survival studies and other methods.

Latent haemolytic anaemia has been described in acute infections and in neoplastic conditions. Brown *et al.* (1944) have detected it in various types of acute sepsis by demonstrating increased elimination of transfused red cells. Brown (1950) has confirmed this finding in six further cases of anaemia of sepsis by transfused red cell survival experiments and has emphasized the latent character of the haemolysis by showing an absence of reticulocytosis or increased faecal urobilinogen excretion. In chronic leukaemia, also, the presence of a latent haemolytic mechanism has been shown (Berlin, 1951) by transfused red cell survival studies on 17 patients; and similar observations on a case of myelomatosis are recorded by Brown and his associates (1944).

In several conditions that may be aetiologically allied to rheumatic fever, evidence of a latent haemolytic mechanism has also been discovered. Brown *et al.* (1944) found a markedly diminished survival rate of transfused red cells in a case of disseminated lupus erythematosus with arthritis. Emerson (1948) described elimination of donor erythrocytes which was three times the normal rate in a case of acute nephritis and this was associated with a gross fall in the haematocrit readings and in the red blood count. Gardner (1952) has made a similar observation in a case of chronic nephritis. Loge *et al.* (1950) have also demonstrated a latent haemolytic mechanism in patients with chronic nephritis and azotaemia. This was similar to the haemolytic mechanism described in the present investigation in that it was disclosed by the means of studies on the survival of transfused red cells, although the serum bilirubin and faecal urobilinogen output were normal, and the Coombs test was negative. In two cases of rheumatoid arthritis increased destruction of donor cells has been reported (Mollison and Paterson, 1949), 50% being destroyed in 22 days in one case.

Studies on the survival of transfused red cells show a significant difference between the survival at 10 and 20 days after transfusion of donor red cells in cases of rheumatic fever compared with a control series having normal survival times. Moreover, the slope of destruction of these cells in cases of rheumatic fever is curvilinear, indicating the presence of a haemolytic mechanism destroying red cells irrespective of their age. It might seem possible that these changes could be accounted for by changes in plasma volume, and that in fact the anaemia is merely due to haemodilution. Reid, Watson and Sproull (1950) claim that there is an increase in plasma volume in the acute stage of rheumatic fever. In seven cases that they investigated the plasma volume was higher than would be expected from the body weights of the patients. On salicylate therapy there was a sharp increase in the plasma volume followed eventually by a fall in plasma volume as recovery took place. No study of the serial changes in plasma volume was made in untreated cases. This seems to cast some doubt on their contention that the untreated disease, when in the acute phase, is associated with an increase in plasma volume. Six out of their seven cases had in fact been treated with sodium salicylate before their investigation in hospital; and as the serum salicylate level was not estimated on these cases at the time of the initial plasma volume estimation, it is possible that the initial raised reading might have been due to a sodium effect. Hecht and Jager (1947) have shown a 22% increase in plasma volume due to the ingestion of large doses of sodium salicylate. Moreover, in many of Reid's patients, as was almost always the case in the patients studied in this investigation, the acute phase of the disease was accompanied by a fall in body weight, and this

in itself is surprising if there were a progressive increase in plasma volume over this period, although it might be accounted for by changes in distribution of the body water. York and Fischer (1947) showed no increase in plasma volume in six untreated cases of rheumatic fever, but when sodium salicylate was given five cases had an increase in plasma volume; the authors suggest that this was a direct result of sodium ingestion. It has been suggested that an increase in plasma volume in rheumatic fever is the sole cause of the anaemia, by means of haemodilution (Cochran, 1951). This would not account for the findings in the survival studies of transfused red cells. The immediate post-transfusion donor cell count would be artificially low if this were related to an increase in plasma volume. Now in all in the present series save for E.D. (2), blood transfusion was given at the peak of activity of the disease, and in six cases there was progressive improvement with a fall in the sedimentation rate in the ensuing 20 days. As it is suggested that the plasma volume diminishes as the sedimentation rate falls and recovery takes place, there should be an increased concentration of donor red cells during this period, rather than a diminishing donor cell population.

It will be noticed from the curves of elimination of transfused red cells that, in those cases that were treated with a short course of salicylate, there was no related increase in the elimination of transfused red cells. If York and Fischer's suggestion is correct and changes in plasma volume in cases of rheumatic fever treated with salicylate are due to a sodium effect, this observation is understandable, because nearly all these patients were given salicylate in the form of calcium aspirin. It seems very unlikely, therefore, that the slope of elimination of transfused red cells bears any relation to changes in plasma volume, if indeed such changes occur in cases of rheumatic fever not treated with sodium salicylate.

The finding that normal red cells are destroyed by an abnormal haemolytic mechanism in the circulation of patients with acute rheumatic fever makes it unnecessary to postulate that the anaemia is due to increased destruction of faulty red cells produced by a bone marrow damaged by the disease. To prove this contention conclusively it would be necessary to transfuse blood from rheumatic patients into normal recipients and to show that its mean red cell survival was normal; such an experiment was considered to be unjustifiable in view of our ignorance of the cause of the disease and the possibility of transference of some abnormal process by this means.

The degree of increased red cell destruction, as shown by the slope of elimination of donor red cells, is in no instance very great; therefore gross signs of haemolysis are not likely to be present and the process may be defined as a latent haemolytic mechanism. Although investigations of the Coombs test have not identified any immune body reaction in rheumatic fever, some such mechanism would seem to be the most likely cause for the haemolysis. The recent work of Glynn and Holborow (1952) has demonstrated the presence of auto-antibodies in rabbits that have developed arthritis and rheumatic fever-like lesions following injection with a polysaccharide-streptococcus vaccine. This observation may be related to the mechanism of the production of haemolysis in patients with acute rheumatic fever.

Summary

The rapidity of the onset of anaemia in acute rheumatic fever suggests an underlying haemolytic process.

The survival of transfused red cells has been followed in six control cases and in eight children with acute rheumatic fever. In the control cases disappearance of donor red cells from the recipient's circulation occurred at a steady rate with a linear slope of elimination. In acute rheumatic fever there was an increased rate of disappearance of donor red cells with a curvilinear slope of elimination indicating random destruction unrelated to the normal process of ageing.

It is concluded that the anaemia in acute rheumatic fever is due, at least in part, to a haemolytic process.

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APPENDIX

Case 1. D.D., a boy, aged 14 years, was admitted to hospital on July 2, 1949, with a history of joint pains and fever for one week and of pleuritic chest pain for three days. His illness started suddenly with pains in the feet, and these rapidly spread to involve the knees, hands and elbows, all joints being involved simultaneously. He had a previous history of three attacks of acute rheumatism involving the joints, apparently without carditis and with no residual joint changes. There was a family history of acute rheumatism.

On admission he had a temperature of 103° F., and sleeping pulse of 125; there was arthritis in the shoulders, wrists and small joints of the hands and feet, generalized lymph node enlargement and enlargement of the liver. There were also signs of consolidation in the right upper zone of the chest and a discrete maculopapular rash on the extensor surfaces of both forearms. The sedimentation rate was 125 mm. in one hour, QTc. 0·452 sec., red blood count 4·5 million, haemoglobin 12·3 g. His blood was group A Rh positive. He exhibited a remittent fever with a high sleeping pulse rate and gross elevation of the sedimentation rate for the first 10 weeks in hospital. During this time he developed a moderately severe anaemia and had a markedly elevated white cell count; his QTc remained prolonged during this period. Nodules appeared over the left elbow two weeks after admission and he developed pericarditis on August 9. Shortly after this, mitral and aortic diastolic murmurs became audible. He was transfused with 450 ml. of group O Rh-positive packed red cells, two days old, on August 8 with no untoward reaction. At this time the disease was still very active, the sedimentation rate was grossly elevated, and arthritis and pericarditis were all present shortly after transfusion. From the tenth week, however, the disease started to subside, the arthritis disappeared, the QTc became normal and the fever and sedimentation rate settled, but on October 12 he had a severe relapse with arthritis and olecranon bursitis, a sharp rise in sedimentation rate accompanied by slight fever, and prolongation of the QTc. This episode subsided quite rapidly but he continued to run a course of chronic low grade activity and he was in this condition when the investigation of his transfused cell survival rate was completed. A direct and indirect Coombs test on August 5 was negative; serum bilirubin 0·4 mg. %, reticulocytes 1%, osmotic fragility of red cells (Creed's technique), trace of haemolysis at 0·48% NaCl, but otherwise normal.

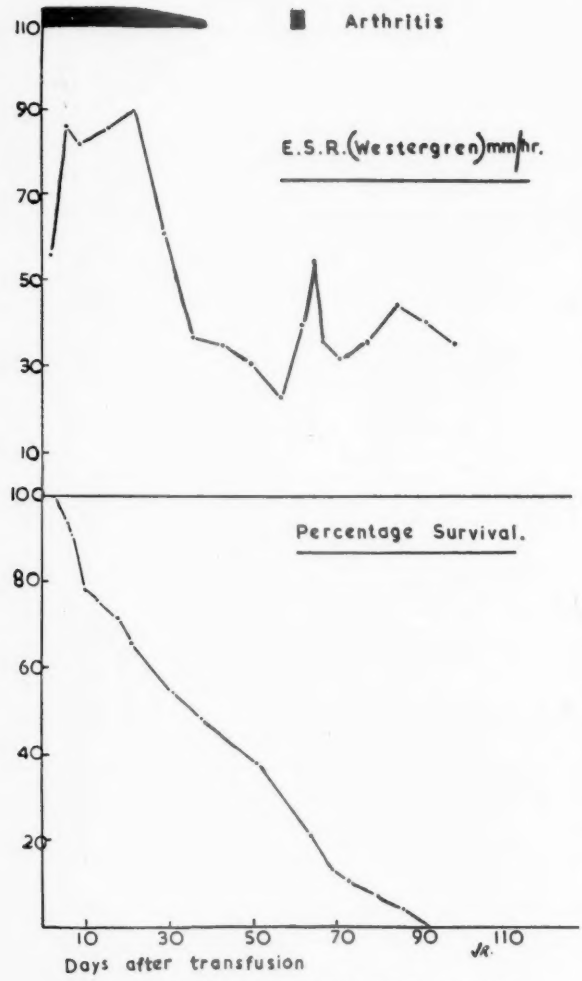

FIG. 3.—Survival of transfused red cells in Case 1.

The percentage survival of transfused red cells in this case, plotted against the erythrocyte sedimentation rate, can be seen in Fig. 3. The slope of elimination during the first 20 days after transfusion was considerably steeper than normal but following this period the slope tended to flatten out until the fiftieth day after transfusion when it again took on a steeper slope only to flatten out again from 70 days until the time of total elimination at 94 days.

Case 2. B.T., a boy, aged 12 years, was admitted to hospital on October 15, 1949, with a one-day history of severe pain in the legs and right arm, and swelling of the right knee. He had a sore throat three weeks before the onset of these symptoms.

On admission he had a fever of 103° F. and severe arthritis involving the knees, ankles and small joints of the right foot; the spleen was enlarged and firm, 2 cm. below the left costal margin. The sedimentation rate was 96 mm. in one hour; QTc 0·426 sec.; red blood count 4·0 million per c.mm.; haemoglobin 12·6 g.; packed cell volume 35 c.cm. %; white blood count 26,000 per c.mm. (94% polymorphonuclear leucocytes). His blood was group A, Rh positive. A Coombs test, direct and indirect, was negative. The arthritis continued for 17 days and then subsided spontaneously. On the fifth day of admission a basal early diastolic and an apical mid-diastolic murmur were heard for two days and there was considerable prolongation of the QTc. He was febrile for the first three weeks and had a high sedimentation rate, and the haemoglobin had fallen to 11·1 g. by the sixth day. On October 20, six days after

the estimated onset of the disease, he was transfused with 500 ml. of group O Rh-positive packed red cells without any untoward reaction. From the third week onwards he showed signs of recovery with subsidence of fever and of the raised sedimentation rate, which returned to normal at the end of the seventh week of his stay in hospital. He also started to gain weight, and the diastolic murmurs in the heart became inaudible. The percentage survival of transfused red cells in this case is shown in parallel with the sedimentation rate (Fig. 4). During the first 15 to 20 days after transfusion the rate of donor cell destruction was considerably increased above the normal, corresponding to the period of greatest activity of the rheumatic fever with arthritis, carditis and a high sedimentation rate. Faecal urobilinogen excretion over the three-day period (October 26 to 28) gave a mean value of 130 mg. per 24 hours and the haemolytic index was raised to 41. Repeated estimation when the disease was inactive gave a mean 24 hour excretion of 26 mg. and a haemolytic index of 5·5.

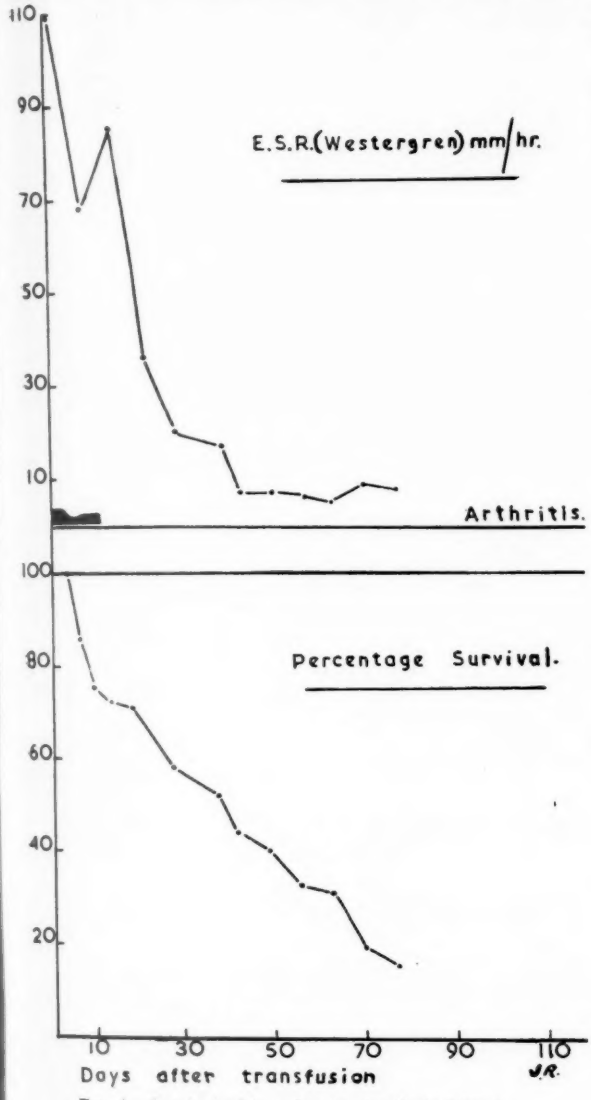

FIG. 4.—Survival of transfused red cells in Case 2.

Case 3. D.N., a boy, aged 12 years, was admitted to hospital on November 18, 1949, with an eight-day history of pains in the right ankle, left knee and in both wrists, associated with fever. This illness was preceded by scarlet fever which started on October 2, 1949.

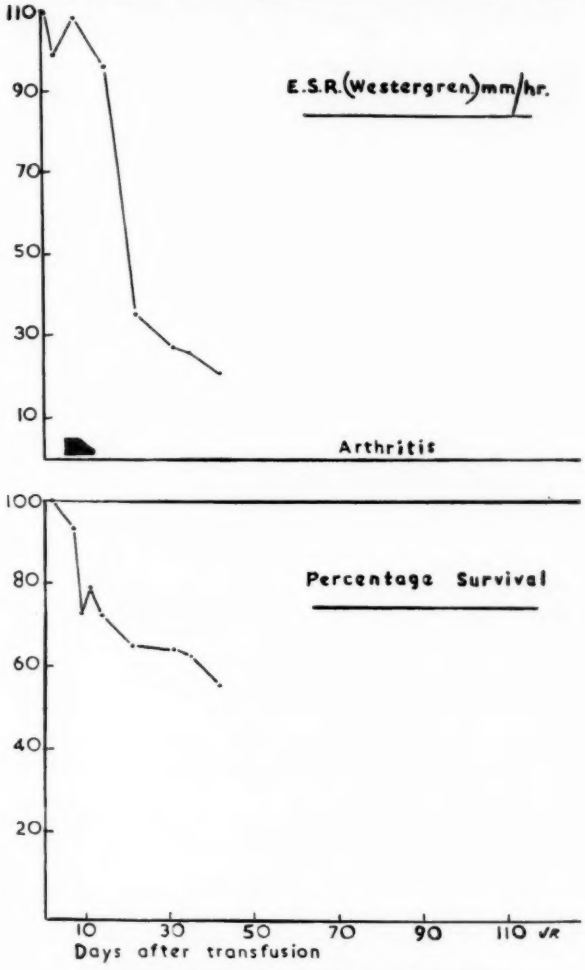

FIG. 5.—Survival of transfused red cells in Case 3.

On admission the patient had fever up to 102° F. at night, arthritis in the left knee, a long, early rather loud systolic murmur at the apex and a short early basal diastolic murmur. The spleen was palpable 2 cm. below the left costal margin for the first month and it was firm in consistency. An apical mid-diastolic murmur developed on the fourth day after admission to hospital and was heard constantly after this. The sedimentation rate was 107 mm. in one hour; QTc 0·401 sec.; red blood count 4·0 million per c.mm.; haemoglobin 11·5 g.; white

cell count 8,250 per c.mm. (66% polymorphonuclear leucocytes), packed cell volume 30 c.cm. %. He was treated with salicylates, 6 g. daily, for 10 days with subsidence of fever and dispersal of arthritis. The apical and basal diastolic murmurs remained constant and the QTc was prolonged beyond the limits of normal, on several occasions. On the fifteenth day after admission four days after stopping salicylate therapy, there was a recurrence of arthritis and fever and a slight rise in sedimentation rate and QTc. This relapse lasted for eight days after which it subsided spontaneously with a rapid fall in sedimentation rate. On November 28, 18 days after the estimated onset of the disease, he was transfused with 500 ml. of group O Rh-positive packed red cells, two days old, without any reaction.

The survival of donor cells was only estimated for 42 days after transfusion, but by this time the patient's condition was almost normal. There was considerably increased destruction of transfused red cells in the first 15 to 20 days corresponding to the period when the sedimentation rate was high and the patient had severe arthritis and active carditis (Fig. 5).

Case 4. C.C., a boy, aged 11 years, was admitted to hospital on November 4, 1949, with a history of joint pains involving both knees and the left ankle for four days, the left knee being swollen and immobile. There was a past history of rheumatic fever with carditis one year previously.

On admission his temperature was 102° F. and he had arthritis of both knees and both ankles. There were no diastolic murmurs on auscultation but he had a pericardial friction rub which was present for two days. The spleen was just palpable. His sedimentation rate was 98 mm. in one hour; red blood count 4·0 million per c.mm.; haemoglobin 11·3 g. and white cell count 12,000; QTc 0·402 sec. His blood was group B Rh-positive. Polyarthritis, fever and tachycardia persisted for the first four days and on November 8 calcium aspirin therapy, g. 5 daily, was started. Following this, there was rapid relief of arthritis with subsidence of fever and of tachycardia. On November 9 a mitral diastolic murmur was heard for the first time and a few days later an aortic diastolic murmur also became audible. On November 12, 12 days after the estimated onset of the disease, he was transfused with 300 ml. of group O Rh-positive packed red cells with no subsequent reaction. Salicylates were stopped on November 17 and two days later he had a recurrence of fever, tachycardia and arthritis and his sedimentation rate rose from 75 to 106 mm. in one hour. There was a fall in haemoglobin accompanying this relapse. He remained febrile with persistent arthritis and a grossly prolonged sedimentation rate for the next six weeks, although there was gradual improvement in his condition towards the end of this period. Survival of transfused red cells was studied in this case for 48 days after transfusion. The case is unique in this series in that during the whole period of the experiment the rheumatic fever ran a course of acute activity and only showed some tendency to recovery in the past fortnight. The slope of elimination of donor cells was fairly steep throughout the whole 48 days (Fig. 6) although in the last 14 days there appeared to be some flattening out of the curve. Thus the complete slope of elimination is again curvilinear.

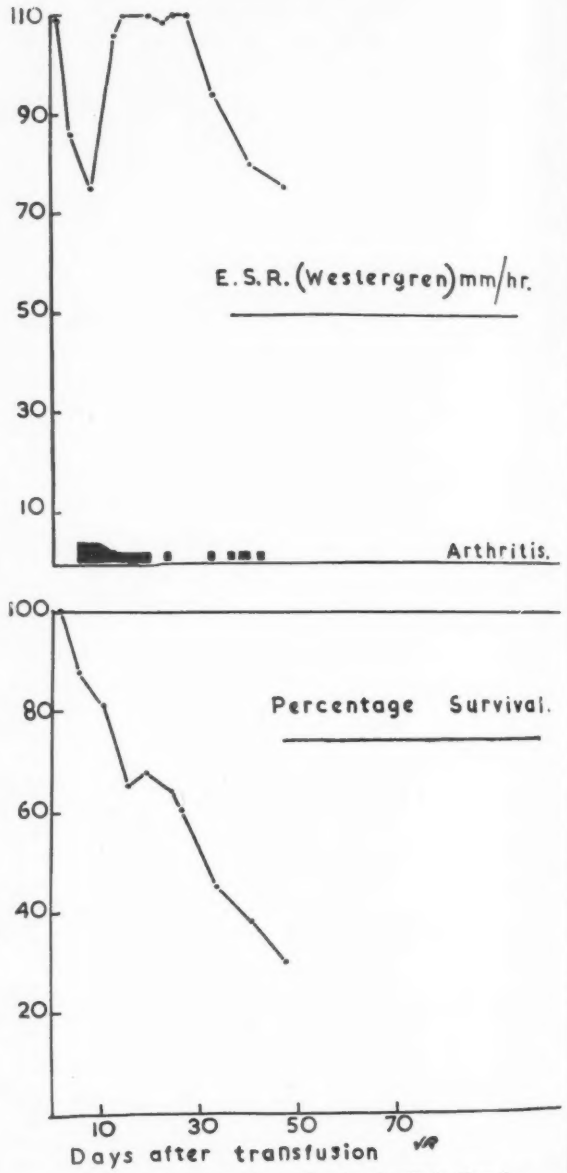

FIG. 6.—Survival of transfused red cells in Case 4.

Case 5. A.F., a girl, aged 6 years, was admitted to hospital on May 27, 1949, with a history of transient pain in one ankle six days previously, followed by substernal pain on breathing three days later and pains in the feet and legs on the day before admission. On the day after admission she developed arthritis in both knees, erythema marginatum and chorea with a high fever and sedimentation rate of 87 mm. in one hour. Three days

later an apical mid-diastolic murmur was first heard and the QTc was prolonged to 0·437 sec. She was treated with calcium aspirin, g. 3 daily, for nine weeks, and this rapidly controlled the fever and joint pains. On admission the red blood count was 4·8 million, haemoglobin 12·1 g. and her blood was group A Rh-positive. She was transfused on June 13, 23 days after the estimated onset of the disease, with 400 ml. group O Rh-positive packed red cells with no reaction. The fever, QTc and sedimentation rate had settled to normal five weeks after admission and the apical mid-diastolic murmur and chorea disappeared two weeks later. Following this the disease ran an uneventful course to complete recovery.

Survival of transfused red cells was studied in this case until complete elimination occurred at 94 days. Although the disease settled down more rapidly in this case than in those previously described, there was increased donor cell destruction initially followed by a flattening out of the slope of elimination (Fig. 7).

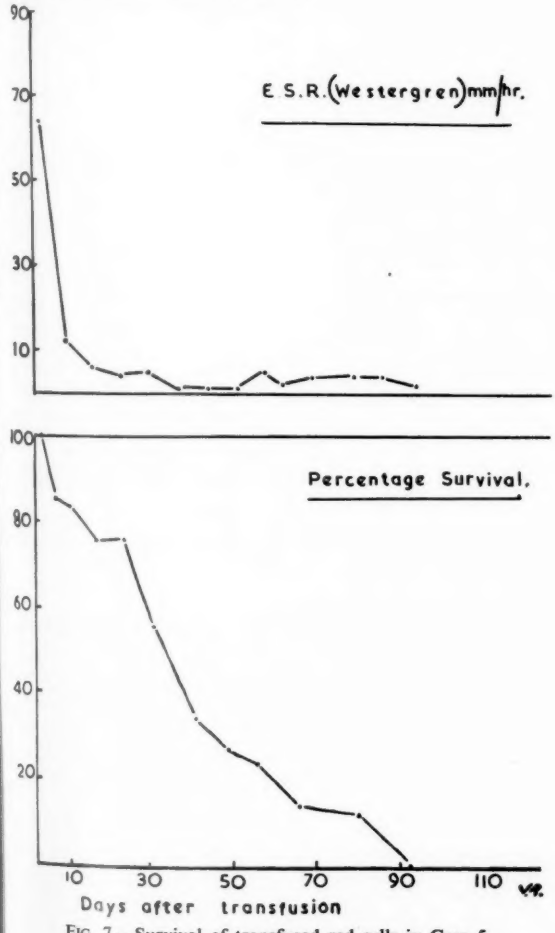

FIG. 7.—Survival of transfused red cells in Case 5.

Case 6. P.B., a girl, aged 13 years, was admitted to hospital on March 31, 1949, with a history of pains in the wrists, knees and small joints of the feet for five days associated with fever and marked pallor. On admission she had a fever of 103° F. at night which persisted for 10 days, severe arthritis in the knees, ankles and fingers, and a significant apical systolic murmur with apical and

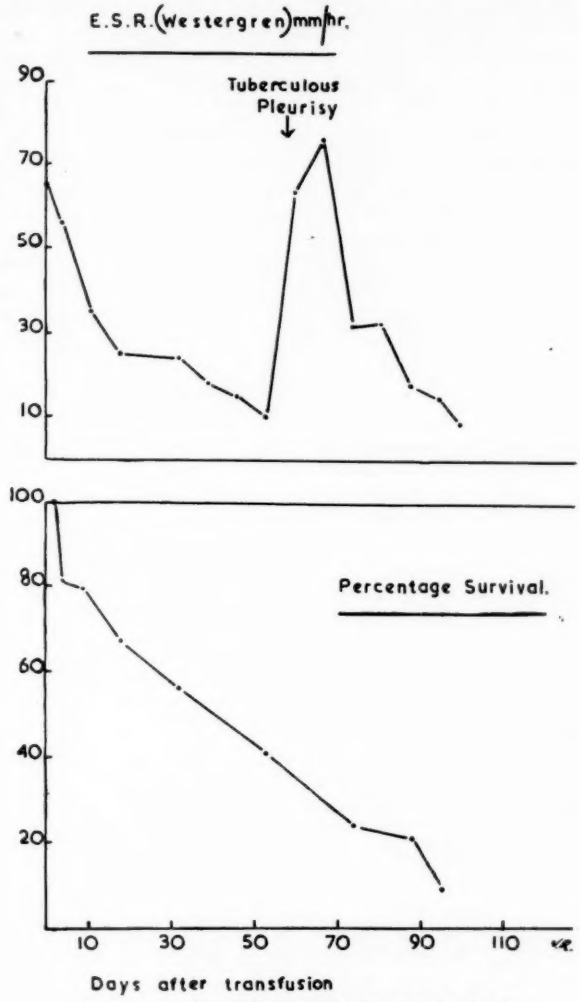

FIG. 8.—Survival of transfused red cells in Case 6.

basal diastolic murmurs developing on the fifth day after admission. Sedimentation rate was 107 mm. in one hour, QTc 0·441 sec., red cell count 4·0 million per c.mm., and haemoglobin 11·5 g. and white cell count 20,000 (85% polymorphonuclear leucocytes). Her blood group was A Rh-positive.

The apical mid-diastolic murmur disappeared in the third week and was only heard subsequently for a short time from the thirteenth to the seventeenth week in hospital; the early basal diastolic murmur was heard constantly. The sedimentation rate fell to normal in the twelfth week, but rose again sharply in the next week with an attack of diaphragmatic pleurisy. This was thought to be non-rheumatic as there was conversion of the Mantoux reaction from negative to positive following this episode. There were no signs of rheumatic activity

from this time onwards. The patient was transfused on April 22, 26 days after the estimated onset of the disease, with 450 ml. of group O Rh-positive packed red cells with no subsequent reaction. Immediately before transfusion the red blood count was 3·6 million; haemoglobin 10·3 g.; packed cell volume 31 c.cm. %. Two days after transfusion the red blood count was 4·9 million, haemoglobin 13·7 g.; packed cell volume 41 c.cm. %, and reticulocytes 3%.

The survival of donor cells was followed for 95 days after transfusion. Initially there was increased donor cell destruction for the first 20 days after transfusion, after which the slope of elimination became flatter and conformed with the normal. It is interesting that when the patient developed tuberculous diaphragmatic pleurisy 60 days after transfusion with fever and a sharp rise in sedimentation rate, there was no apparent increase in the rate of elimination of donor cells. This is in contrast to the increased elimination of donor cells in rheumatic relapse (Fig. 10). The slope of elimination is curvilinear initially with the steepest portion of the curve corresponding to the period of acute rheumatic activity.

Case 7. E.D., a girl, aged 6 years, was admitted to hospital on December 15, 1948, with a history of severe joint pains in the right hip and right knee of one day's duration following a sore throat three weeks earlier. An apical mid-diastolic murmur and an early basal diastolic murmur were heard on the first day of admission and persisted throughout her illness. She was choreic and developed rheumatic nodules over the right elbow and there was low grade pyrexia and a persistently raised sedimentation rate for the first 15 weeks in hospital. On March 27, 1949, she had a relapse with a raised temperature and sleeping pulse rate, erythema marginatum and an increase in activity of carditis as indicated by prolongation of the QTc from 0·444 sec. to 0·474 sec. She developed arthritis in the left hip on March 30. Three days later, at the height of this relapse, she was transfused with 500 ml. of fresh group O Rh-positive packed red cells over a period of eight hours. During the relapse and for the next three weeks she was treated with calcium aspirin g. 2 daily. On May 2 she developed tonsillitis with a rise in temperature and sleeping pulse rate and with elevation of the sedimentation rate. Salicylates were given for a further two weeks, but seven days after they were stopped, on May 17, she again relapsed with fever and arthritis in the left elbow and in both wrists. Following this the disease settled uneventfully whilst the patient was on continuous aspirin therapy. A further transfusion of 400 ml. of fresh group O Rh-positive packed red cells was given on July 29 with no reaction. Twenty-one days later, soon after stopping salicylate therapy, she again had a rise in temperature and sleeping pulse, a steep rise in sedimentation rate, a recurrence of chorea and of erythema marginatum and a rise in QTc from 0·404 sec. to 0·434 sec. After this, the sedimentation rate slowly returned to normal, but she had an occasional rise in evening temperature and the QTc remained elevated above normal for several weeks.

Survival of donor red cells from the first transfusion was estimated until complete elimination occurred 90 days after transfusion (Fig. 9). This period was marked

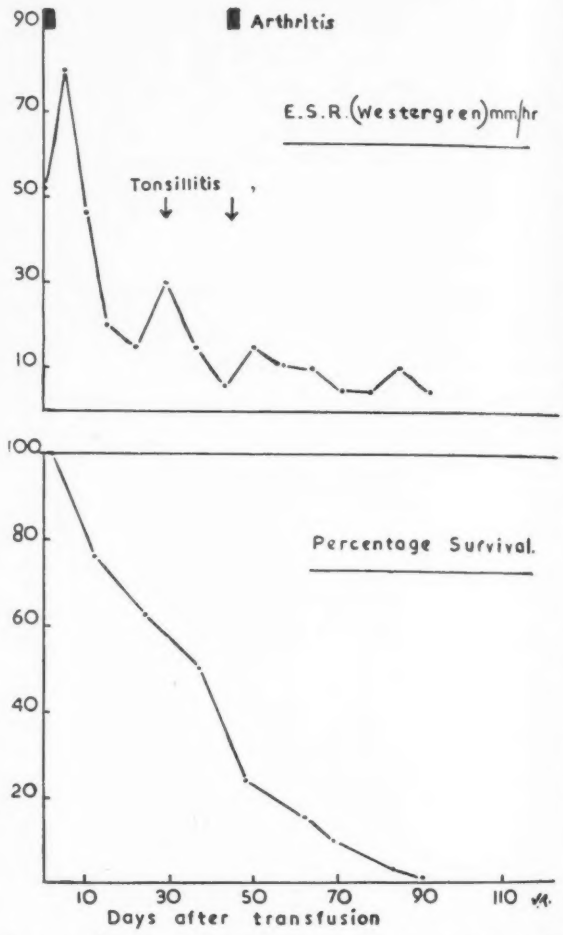

FIG. 9.—Survival of transfused red cells in Case 7, following first transfusion.

by three episodes: at the time of the transfusion the patient was undergoing a severe relapse, 30 days after transfusion she had tonsillitis and 45 days after transfusion she had a further relapse of a milder nature. Immediately before transfusion the red blood count was 4·3 million per c.mm.; haemoglobin 12·7 g.; packed cell volume 41%; reticulocytes 0·8%; serum bilirubin 0·2 mg. %. Direct and indirect Coombs tests were negative and osmotic fragility of the red cells in saline was normal.

There was increased destruction of donor cells in the first 12 days after transfusion, after which there was some flattening of the slope of elimination coinciding with clinical improvement in the patient's condition. The attack of tonsillitis was apparently not accompanied by any increased destruction of transfused red cells, but the relapse at 45 days after transfusion caused a further

increase in steepness of the slope of elimination, which subsequently flattened out again from 50 days onwards. The complete slope of elimination thus forms two curvilinear curves coinciding with the two rheumatic relapses and indicating increased donor cell destruction accompanying these episodes.

The second transfusion was given when the disease had apparently become inactive, with a view to estimating the normal transfused red cell survival in this case, and the first three readings obtained up to 21 days after transfusion appeared to follow the normal line, although they were rather higher than those usually found (Fig. 10). Twenty-two days after transfusion, however, the disease relapsed and an inagglutinable count taken six days later, together with two further counts in the next six days, all showed evidence of considerably increased donor cell destruction coinciding with this episode. Following recovery from this relapse, the slope of elimination flattened out again to conform with the normal. The slope of elimination coinciding with the clinical relapse is curvilinear.

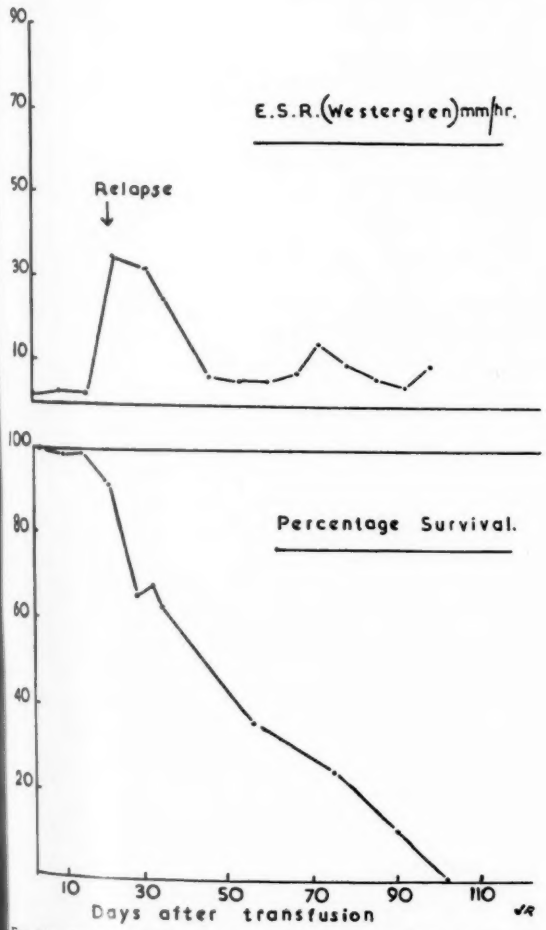

FIG. 10.—Survival of transfused red cells in Case 7, following second transfusion.

This case is of particular interest for, following both transfusions there was a relapse, and accompanying each relapse there was increased elimination of transfused red cells.

Case 8. B.R., a girl, aged 10 years, was admitted to hospital on February 22, 1949, with a four month's history of recurrent joint pains following a sore throat.

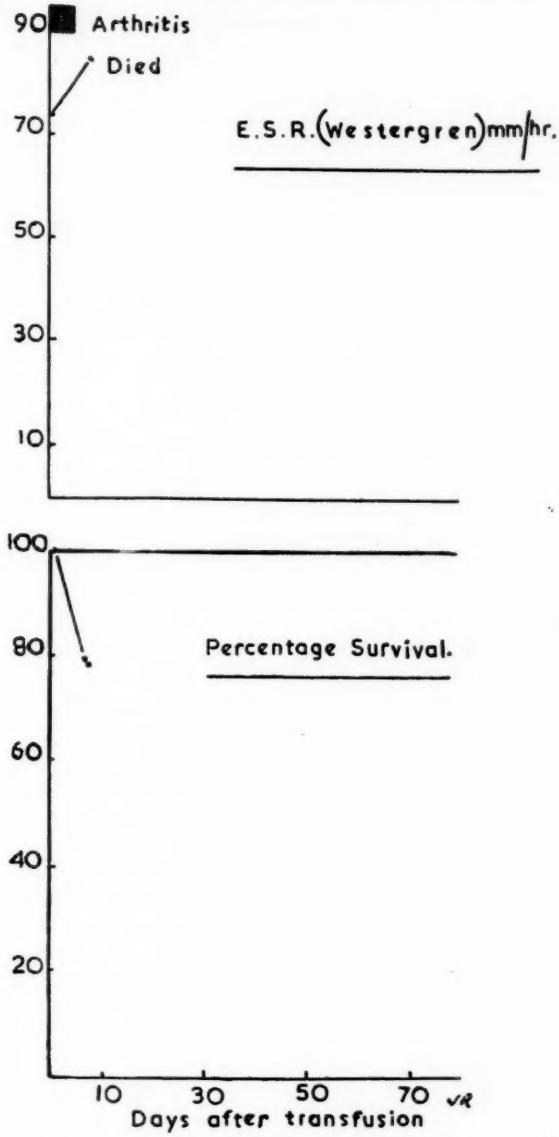

FIG. 11.—Survival of transfused red cells in Case 8.

She had a past history of several attacks of rheumatic fever, the first occurring at the age of 4, and from August 1, 1947, until February 29, 1948, she was in hospital with rheumatic carditis and mitral and aortic valve disease.

On admission she had large nodules on the elbows,

knees and occiput. There were loud apical systolic and diastolic murmurs and a loud early diastolic murmur was audible over the base of the heart. The sedimentation rate was 31 mm. in one hour and the QTc was 0·428 sec. She had a moderate anaemia with 4·0 million red cells, haemoglobin 11·1 g. and her blood was group A Rh-positive; osmotic fragility of red cells was normal. Three days after admission she had a severe relapse with arthritis, a high temperature and sleeping pulse rate, pericarditis and severe epistaxes; her sedimentation rate rose to 56 mm. in one hour. The QTc rose to 0·436 sec., but with the onset of pericarditis it fell progressively to 0·303 sec. The degree of anaemia rapidly increased, and three weeks after the onset of the relapse the red cell count was 2·9 million, haemoglobin 7·3 g. and packed cell volume 23%. The reticulocyte count was 2·2%; serum bilirubin 0·8 mg. %; and there was excess of urobilinogen in the urine. Osmotic fragility of red cells, trace of haemolysis in 0·48 per cent. saline. On March 23, 1949, 26 days after the relapse, she was transfused with 300 ml. of group O Rh-positive packed red cells, four days old, in nine hours. On March 26, she had a further relapse with arthritis and pericarditis and she died on April 4 in congestive cardiac failure. Necropsy revealed severe rheumatic carditis with gross involvement of the aortic valve, which was incompetent, and lesser involvement of the mitral valve; there was also evidence of acute rheumatic pericarditis with effusion. The spleen weighed 102 g. and the sectioned surface looked normal It was only possible to follow the survival of transfused red cells for seven days after transfusion in this case owing to the death of the patient. In this period, however, there was marked increased destruction of donor red cells, 79·1% surviving after seven days (Fig. 11). During this time the patient was severely ill and in cardiac failure so that only two inagglutinable counts were obtained following the initial donor cell count. The more rapid fall in the donor count in this case compared with the previous cases might be accounted for to some extent by an increase in plasma volume associated with cardiac failure.

PRIMARY TUBERCULOSIS IN AFRICAN CHILDREN

BY

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The patients who comprise the clinical material for this investigation were all African children admitted to the medical wards of King George VI Hospital during the period August, 1952, to September, 1953, inclusive. Most of the children were Wakikuyu (78%) and came from the native reserves or from the African locations in Nairobi. It has been found impossible to divide them into rural and urban groups owing to the large number of accommodation and fictitious addresses given by the parents. It is known that a considerable proportion of those who gave a Nairobi address had in fact come from the reserves a few days previously.

It was an established routine that every child on admission to hospital had a Mantoux test performed, the site of injection being examined at 48 hours and thereafter daily for a further three days. The injection consisted of 0·1 ml. of 1 in 1,000 old tuberculin (Burroughs Wellcome), the solution being freshly prepared in the Medical Research Laboratory, Nairobi. The diluting fluid used during the period of this investigation was 0·5% carbol saline. It is often difficult to detect an erythematous reaction in the darkly pigmented skin of an African, and in this series the presence of palpable induration of the skin was used to determine positive reactors.

In cases where the reaction was in doubt, and in those patients who were suspected of having tuberculosis but were negative reactors, the test was repeated using a 1 in 100 dilution.

In all, 1,149 consecutive children were tested and the results are shown in Table 1. All children who died or left hospital within 48 hours have been excluded from this investigation.

In this series there were 131 positive reactors and a further 31 patients who had active tuberculosis but were negative reactors to both 1 in 1,000 and 1 in 100 dilutions of old tuberculin. These latter have been recorded as 'false negatives'. Every patient with a false negative reaction was found to have rapidly progressive disease, and in most cases they were suffering from an advanced stage of the disease at the time of admission. All this group of patients died, the majority within 10 days of entering hospital, and the longest period of survival recorded following a false negative reaction was four weeks.

TABLE 1

RESULTS OF MANTOUX TESTS ON 1,149 AFRICAN CHILDREN

Age in Years	No. of Cases	No. of Positive Reactors	No. of False Negative Reactors	Total Positive and False Negative Reactors (%)
Under 1	345	16	4	5·8
1–2	214	14	7	9·8
2–3	191	16	6	11·5
3–4	153	20	4	15·7
4–6	144	26	6	22·2
6–8	71	23	2	35·2
8–10	31	16	2	58·1

Among the 131 positive reactors there were 18 children (13·7%) who showed a hypersensitive reaction to the 1 in 1,000 Mantoux test. In these children, the site of the injection showed vesiculation at 48 hours, which led to ulceration, the lesion usually being a half to one inch in diameter. No particular age group was affected, but 17 out of the 18 cases showed evidence of an active lesion.

Of 162 infants and children who were either positive or false negative reactors, 132 (101 positives and 31 false negatives) were investigated with a view to assessing the activity or quiescence of the disease. Whenever possible each child had a radiograph taken of the chest, an examination of the sputum or gastric washings for tubercle bacilli, and a sedimentation rate (Westergren) estimation, in addition to routine charting of weight and temperature. The results obtained are shown in Table 2.

TABLE 2

ASSESSMENT OF ACTIVE TUBERCULOSIS IN MANTOUX-POSITIVE AND FALSE-NEGATIVE REACTORS

Age in Years	No. of Cases	No. with Active Tuberculosis	No. with Quiescent Tuberculosis
Under 1	16	16 (7 died)	Nil
1–2	21	21 (16 „)	Nil
2–3	22	22 (10 „)	Nil
3–4	16	14 (5 „)	2 (both doubtful)
4–6	24	20 (7 „)	4 (one doubtful)
6–8	24	15 (3 „)	9 (one doubtful)
8–10	13	8 (4 „)	5

Nine children are included in Table 2 who were taken out of hospital by their parents, but whose condition was deteriorating so rapidly that their expectation of life could not reasonably have been expected to exceed a week. (It has been assumed that these children died.)

It seems likely that the death rate in the under-1-year-old group may be artificially low. The mothers of these infants were admitted as well as their infants in order that breast feeding might be maintained. Several mothers discharged themselves and their infants prematurely before the outcome of the infection could be determined.

The very high mortality rate during the second and third years of life is probably due to a great extent to the very poor standard of nutrition which is general in this age group among African children. Kwashiorkor and other nutritional diseases in particular occur in this section of the population, as the children are deprived of many of the basic necessities of life. Infants over 1 year old have to learn to fend for themselves as their mothers are often occupied with a more recent addition to the family. The state of emaciation and semi-starvation of these young children provides little resistance to infection with the tubercle bacillus, and they succumb to the disease very readily.

Clinical Findings

The clinical features of children with active primary tuberculosis show certain differences from those found in European children. Forty-one children, selected as having active primary lesions, have been kept under observation in hospital and as out-patients during the last 15 months. It is hoped that a preliminary report will be published shortly on the natural history of primary tuberculosis in the African child in Kenya, based on these selected cases.

Several of these children were discovered as a result of showing a positive reaction to the tuberculin test, and if this had been omitted there would have been no reason to suspect an active primary infection as there were no symptoms suggestive of the disease. Most of the children, however, appeared ill, the commonest symptoms being lassitude and mental apathy, combined with fever, a harsh, dry cough, anorexia and loss of weight.

Fever was a particularly prominent symptom. In 14 patients (34%) the temperature on admission was in excess of 102° F., and usually remittent in character. There were only 10 patients (24%) in the series whose temperature remained persistently below 100° F. The degree of pyrexia appears to be considerably greater than that found in children in the United Kingdom, where there is usually only a low-grade irregular fever of 99 to 100° (Sheldon, 1943; Paterson and Moncrieff, 1947a).

Radiological Findings

The most constant feature found on radiographic examination of the chest in these children was

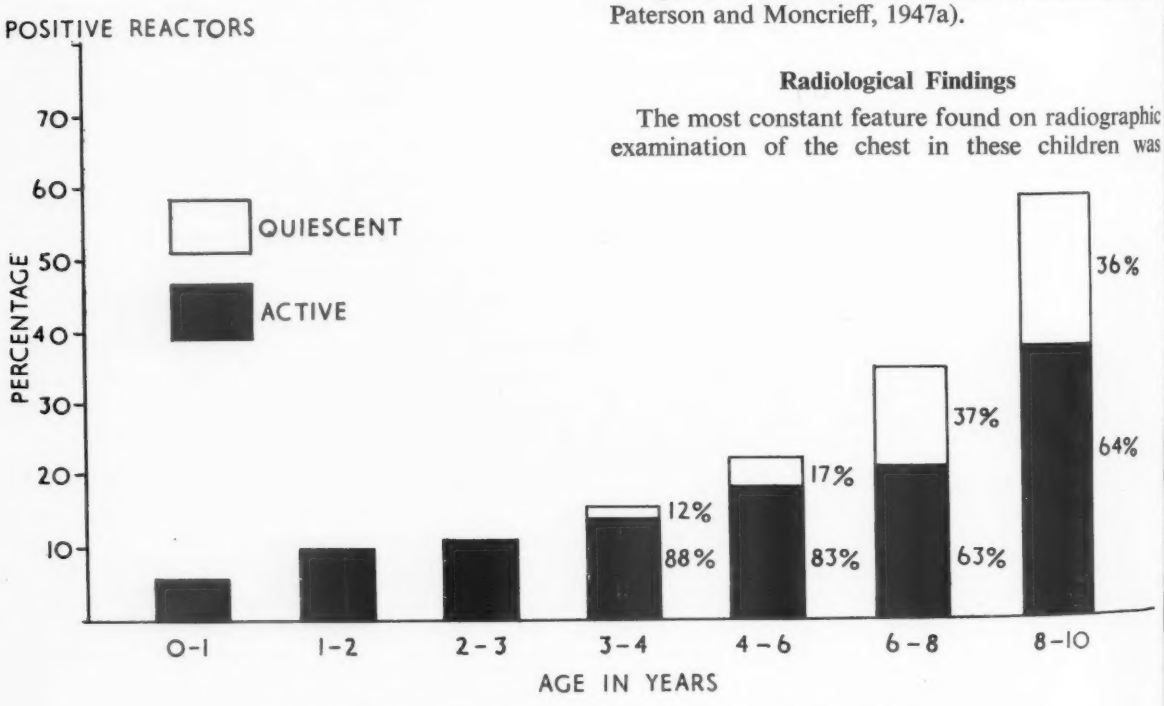

FIG. 1.—The incidence of active tuberculosis among tuberculin reactors.

enlargement of the hilar glands. This was present in 40 (97·5%) out of 41 patients, and the glandular enlargement was of a very considerable degree in 24 (58·5%) of them. It may be suggested that as these children were selected patients they might have been selected on account of the enlarged hilar glands, thereby raising the proportion of patients with glandular enlargement. The selection of cases, however, depended on the patients being free from other disease, which, by its nature, might interfere with the natural progress of the tubercular lesion. For this reason one patient was removed from the series on account of typhoid fever, which would have invalidated the temperature chart, if nothing else. During the course of the investigation all children were accepted as suitable provided there was no evidence of the development of a tuberculous bronchopneumonia, miliary spread or tuberculous meningitis when the child was examined initially. On a number of occasions children were tentatively accepted for inclusion in the series on account of a positive tuberculin test and an otherwise unexplained fever before a radiograph had been taken.

Opacities extending out from the root of the lung were also frequently encountered. These lesions, previously described as epituberculous, but more recently considered to be due to absorption collapse (Graham and Hutchison, 1947) or collapse-consolidation (Adler and Richards, 1953), were present to a varying degree in 28 patients (68%). Table 3 shows the distribution of these opacities, which were all either segmental or lobar in extent.

TABLE 3

FREQUENCY OF COLLAPSE-CONSOLIDATION IN DIFFERENT LOBES

Right upper lobe	3 cases
Right middle lobe	10 ,,
Right lower lobe	2 ,,
Left upper lobe	2 ,,
Left lower lobe	4 ,,
Right upper and right middle lobes	3 ,,
Right upper, right middle and right lower lobes	1 case
Left upper and left lower lobes	1 ,,
Left upper and right middle lobes	1 ,,
Left upper and right lower lobes	1 ,,

In this series, of 34 lobes involved, the right middle lobe was affected on 15 occasions, the right upper, left upper and left lower lobes on five occasions each, and the right lower lobe four times.

Mode of Death

In those patients who succumbed to the disease, death usually occurred within three months of the first symptom referable to a tuberculous infection, and this is in agreement with the views of Wallgren (1938) and Paterson and Moncrieff (1947b).

In a series of 47 consecutive deaths from tuberculosis among children, the cause of death, as diagnosed on clinical and radiological grounds, was as shown in Table 4.

TABLE 4

CAUSE OF DEATH IN 47 TUBERCULOUS CHILDREN

Tuberculous bronchopneumonia	29 cases
Tuberculous meningitis	11 ,,
Miliary tuberculosis	4 ,,
Tuberculous empyema	1 case (infant aged 5 months)
Tuberculous pericarditis with completely caseous left lower lobe	1 case (infant aged 1 year)
Tuberculous bronchopneumonia of left lung with large cavity in left upper lobe	1 case (infant aged 8 months)

Necropsies were performed on 10 of the patients dying from tuberculous bronchopneumonia, and of these, six were found to have miliary spread which had not been diagnosed during life. In each case, however, it was apparent that the dissemination was of recent origin. Tubercles were most numerous in the liver and spleen, the kidneys having to be examined with care to demonstrate lesions macroscopically. In one of these cases, the miliary spread was of such recent onset that only three tubercles were seen on the surface of the liver, and a very occasional lesion was found on cutting sections through the liver substance. No tubercles were found in either spleen or kidneys in this patient.

Four of the patients dying from tuberculous meningitis were examined at necropsy. In two of them, the only other signs of tuberculosis were enlarged caseating hilar glands, and the other two showed widespread miliary tuberculosis.

Death caused primarily by miliary tuberculosis occurred on only four occasions, and the diagnosis was made radiologically in each instance. This is a very much lower incidence than was found by Graham-Johnstone (1949a) working in the same hospital. In her series of 87 positive reactors in children under 6 years old, 16 patients showed radiological evidence of miliary dissemination and 22 showed exudative or pneumonic lesions. It is possible that the variation may be due to individual differences in interpretation of the radiographs, as it was noticed on several occasions in the present series that a rapidly progressive bronchopneumonia produced numerous, fine, and widespread opacities scattered throughout the lung fields, giving a picture very similar to that of miliary tuberculosis.

Cammock and Miller (1951), in their study of tuberculosis in young children in Newcastle, note that tuberculous meningitis and miliary tuberculosis are the major immediate hazards of primary tuberculosis. It is apparent that tuberculous bronchopneumonia is of much greater importance in Kenya among African children than it is among children in the United Kingdom.

TABLE 5
AGE INCIDENCE IN YEARS AND PRIMARY CAUSE OF DEATH IN 47 TUBERCULOUS CHILDREN

Disease	0–1	1–2	2–3	3–4	4–6	6–8	8–10	Total
Tuberculous bronchopneumonia	3	8	9	–	5	2	1	29
Tuberculous meningitis	–	4	–	1	4	1	1	11
Miliary tuberculosis	–	1	–	–	1	1	1	4
Tuberculous pericarditis	1	–	–	–	–	–	–	1
Tuberculous bronchopneumonia with cavitation	1	–	–	–	–	–	–	1
Tuberculous empyema	1	–	–	–	–	–	–	1

(All children included in Table 5 were either seen in consultation or were directly under the care of the author. A number of deaths recorded in Table 2 are not included.)

Discussion

Mantoux Reaction and Primary Tuberculosis. Biggs (1946) considered primary tuberculosis to be a subclinical disease in that a diagnosis could not be made by a general clinical examination, and that height and weight charts were of no assistance. He came to the conclusion that skin testing with tuberculin was the only efficient way to detect the disease, and that its course should be followed by serial radiographs. Many authors have pointed out the value of the Mantoux intradermal and Vollmer patch tests as an indication of previous infection with the tubercle bacillus, but the tests by themselves do not indicate how recently the infection was acquired and they are of little guidance as to the activity of the disease. Several authors, including Ansell and Soltys (1950), consider that marked reactions favour, but do not prove, active disease. This is in agreement with the findings in the present investigation, where 17 out of 18 patients showing a hypersensitive reaction were proved to have active disease. Graham-Johnstone (1949a) and Haynes (1951a) came to the conclusion that the site of the lesion had a direct bearing on the degree of sensitivity shown by the tuberculin test. The highest percentage of hypersensitive reactors occurred among patients suffering from glandular tuberculosis, and tuberculous lesions of bone were the next most frequent, while pulmonary tuberculosis produced the lowest hypersensitivity rate.

Graham-Johnstone (1949b) tested the tuberculin reactions of 800 infants and children under the age of 6 years at the same hospital in Nairobi, and obtained results very similar to the present investigation. There were 87 positive reactors and six with false negative reactions, giving a combined figure of 11·6% compared with 11·4% in this series. Haynes (1951b), during a survey of tuberculosis in Kenya, tuberculin tested 328 children under 6 years in three different centres in Nairobi, and found 28 (8·6%) positive reactors. These figures are not strictly comparable as one group was drawn from an urban area, and the others were selected groups in that all the children were admitted to hospital. They also differ in that the children came from rural as well as urban districts.

The reactor rate to tuberculin among children admitted to hospital has been investigated by Fleming (1943), who reported that in The Royal Hospital for Sick Children, Glasgow, there were 9·3% positive reactors in children under 4 years, 26·3% in the 4-7-year-old group, and 38·1% in children from 7 to 10 years old. Stewart (1947) in Australia carried out a similar investigation among children admitted to the Perth Children's Hospital. He found a reactor rate of 5% during the second year of life, 20% in the fourth year, 44% in the ninth year and 51% in the thirteenth year. He concluded that the children were being exposed to an abnormal risk of infection, and probably excessively frequently. It appears that a large number of cases in Perth were due to bovine tuberculosis, as Margolis (1951), in repeating the investigation in the same hospital a few years later, showed a considerable fall in the reactor rate, which he considered to be due to the slaughtering of all dairy cattle found to have positive tuberculin reactions in the period between the two investigations. In the Nairobi area bovine tuberculosis is rare. Ginsberg (1953) reports that of 10,838 head of cattle slaughtered in the abattoir at Athi since it was opened in July, 1953, only six have been found affected with tuberculosis.

Myers, Harrington and Garcia Suarez (1945) pointed out that wherever large numbers of contagious cases of tuberculosis are permitted to exist among people or animals without adequate isolation or control, a high percentage of children develop primary tuberculosis. Haynes (1951c) has drawn attention to the higher rate of tuberculin reactors among African adults in urban populations in Kenya compared with those of rural districts, and came to the conclusion that a significant number underwent their primary infection in adult life on coming to work in the towns from the native reserves.

The younger the child, the greater the likelihood

there is that a positive tuberculin test will indicate active disease. Opie (1947) quoted Mourad as stating that in infants under 1 year a positive reaction is invariably associated with active tuberculosis, and that during the second year 88% show clinical evidence of the disease falling to 81% during the third year. Kayne, Pagel and O'Shaughnessy (1948) considered that a child under 2 years with a positive test should be regarded as having a progressive lesion, but from 2 to 5 years the lesion could no longer be regarded as necessarily active. In those over 5 years and in adults they considered that a positive reaction merely indicated that the patient had undergone a tuberculous infection at some period in the past. Similar conclusions were drawn by Ansell and Soltys (1950).

Considerable variation in the incidence of active disease in the same age groups occurs in different parts of the country. At the Royal Aberdeen Hospital for Sick Children, Clark (1951) found evidence of active infection in 56% of city children and 40% of country children under 6 years who were admitted to hospital, but Ounsted and Smallpeice (1951), working in the Children's Department of the United Oxford Hospitals, produced evidence that 80·8% of positive reactors among children of 3 to 7 years old attending hospital had active tuberculosis. They considered that the activity rate fell sharply after the age of 7 years as only 27·9% in the 7-14-year-old group showed active lesions. They drew attention to the fact that variations occurred in the activity rate from place to place, and advised that each district should review its own area in order to assess the problems of treatment and control required.

Radiological Evidence of Primary Tuberculosis. Enlargement of the hilar and mediastinal glands occurred in a very high percentage of the children selected for observation as having active primary lesions. Haynes (1951d), in examining radiographs of 43 children with tuberculosis, found hilar glands enlarged in 30 (69·8%) patients. The patients were not selected in the same manner as in the present investigation, but confirm the opinion that such glandular enlargement is a prominent feature in primary tuberculosis among Africans in this Colony. The occurrence of glandular enlargement appears to vary throughout the world. There is a high incidence among American Indian children (High and Zwerling, 1946), but among positive reactors in children in Minneapolis radiographic examination revealed evidence of significant disease so rarely that its use among young children was discontinued (Myers, 1946). This is in contrast to the findings in Kenya, where radiographic examination of the chest has been found to be a valuable aid to diagnosis.

Segmental and lobar opacities involved the right middle lobe much more frequently than any other lobe, and similar observations were made by Richards (1944) and Brock (1950). Richards found the right middle lobe involved in 23 out of 66 affected lobes, and 60 out of 93 were involved in the series published by Brock, who explained the reason for this preponderance on anatomical grounds. First, the middle lobe bronchus is smaller than those supplying the other lobes and therefore more easily compressible, and secondly, the gland usually responsible for causing obstruction to the middle lobe bronchus drains the right lower lobe as well as the middle lobe, which may thus become enlarged as a result of infection from two different sources.

Mortality Rate. The mortality rate among children with tuberculosis admitted to King George VI Hospital was extremely high, particularly in children under 3 years (see Table 2).

Although the number of cases is comparatively small and can have no statistical significance, the general trend indicates that primary tuberculosis in the African child in Kenya carries with it a fearsome mortality rate. Some of the children included in Table 2 were admitted in a very advanced state of the disease, and it may be criticized that the figures are biased, giving an unduly high death rate. It is, however, frequently quoted that patients who have a collapsed segment or lobe of a lung due to pressure on a bronchus or occlusion by caseous material from the rupture of a gland into a bronchus, have a very favourable prognosis (Graham and Hutchison, 1947). In this series, of 28 patients showing such radiological changes, two developed tuberculous meningitis and two died from tuberculous bronchopneumonia, giving a mortality rate of over 14%.

The onset of tuberculous bronchopneumonia was usually followed by rapid deterioration, death often ensuing within two or three weeks and sometimes within a few days. The rupture of a caseating gland into a bronchus leads to dissemination of tuberculous pus along the bronchial tree. The associated obstruction of the bronchus causes absorption collapse or collapse-consolidation, but the lack of immunity among African children often fails to localize the lesion and the disease extends to bronchopneumonia with a fatal termination. In those races which have acquired immunity the usual course of the disease following the stage of collapse is either complete resolution or residual collapse, which may be associated in either case with bronchial

stenosis and a symptomless bronchiectasis (Veeneklaas, 1952). Tuberculous bronchopneumonia is an infrequent complication of the primary lesion.

In Kenya, however, apart from coastal areas, tuberculosis has been introduced comparatively recently (Haynes, 1951e), and the native population has developed little immunity, with the consequence that fulminating exudative and pneumonic lesions are common sequelae of the primary infection in childhood.

The incidence of tuberculosis among children in England has fallen steadily since the beginning of this century, and Wolman (1952) points out that the chief cause is the fall in the morbidity rate among adults, who are the principal source of infection. This has been due to 'improved measures of prevention, greater care of patients, increased education of the public and a change for the better in the general social and economic conditions of the country'. He found that of 20 children aged 4 years who were positive reactors to tuberculin, the source of infection in 17 was found to be due to direct family contact.

The same principles for the protection of children from tuberculosis apply in Kenya. It must be stressed once again that the adult patient with open tuberculosis in the home is the greatest danger to the child, and efforts to control the disease must aim at the early diagnosis and removal of infectious patients from close contact with uninfected people. The standards of housing and hygiene among the native population are distressingly low in many areas. Much is being done in the Colony to raise these standards. Some of the recommendations put forward by Haynes (1951f) have been implemented. It is hoped that the investigation of B.C.G. vaccination among native children will prove it to be a valuable contribution in the prevention of the disease. The control of the disease, however, rests to a great extent on the degree of cooperation obtained from the Africans themselves and their response to the increasing efforts that are being made to raise their standards of personal hygiene and social welfare.

A satisfactory degree of control of tuberculosis in the Colony cannot be envisaged for many years to come.

Summary

The results are given of Mantoux tests performed on 1,149 consecutive African children admitted to King George VI Hospital, Nairobi. There were 131 positive reactors and 31 false negatives. All children with false negative reactions died.

All positive reactors under 3 years old (59 patients) were found to have active tuberculosis; the activity rate among children of 4 to 6 years was 83% and 62·5% among those of 6 to 8 years.

Fever was a prominent feature among those with active primary tuberculosis. In 14 out of 41 patients the temperature on admission was above 102° F.

Enlargement of the hilar or mediastinal glands was an almost constant radiological feature and was gross in 24 (58·5%) patients.

Opacities in the lung fields of an 'epituberculous' nature were present in 28 (68%) patients, the right middle lobe being involved on 15 occasions.

The mortality rate among the younger children was extremely high, rising to 76% during the second year. Tuberculous bronchopneumonia was the most frequent cause of death, occurring in 29 out of 47 tubercular deaths. Miliary tuberculosis occurred as a primary cause of death four times, but was found to an unimportant extent at necropsy on a number of occasions. Tuberculous meningitis occurred 11 times.

Primary tuberculosis among African children in Kenya carries with it a much less favourable prognosis than is found among races which have developed immunity. It is considered that the frequency of tuberculous bronchopneumonia is an indication of the lack of immunity among the native population.

I am indebted to the Hon. the Director of Medical Services, Kenya, for permission to publish this paper. I should like to thank Dr. Lorna Macdougall for her cooperation and for giving me access to her patients. My thanks are also due to Miss M. Marshall and many other ward sisters who gave valuable assistance in carrying out this investigation. Miss P. M. Allen, Librarian at the Medical Research Laboratory, Nairobi, has rendered much help in the study of the literature.

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THE RELATION BETWEEN BIRTH WEIGHT AND SUBSEQUENT WEIGHT IN CHILDHOOD

BY

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(RECEIVED FOR PUBLICATION JANUARY 7, 1954)

The most recent investigations of the relation of birth weight to subsequent weight (Illingworth, 1950; Illingworth, Harvey and Gin, 1949) have led to the conclusion 'that the birth weight had a constant and very important relationship to subsequent weight at all ages studied (up to 13 years)'. This is an important matter in paediatrics because many assessments of children's growth are based on it. It is therefore essential for the correct interpretation of the result to ascertain whether a generalization as expressed above is justified and, if not, to show in what respects it must be qualified if it is to serve as a useful criterion for judging children's growth. As will be shown, the statement requires qualification in three respects: (1) as regards the extent or intensity of the dependence of subsequent weight on birth weight; (2) as regards the supposed constancy of the relation throughout childhood; and (3) as regards the meaning of such a dependence. To each of these items, one of the following sections is devoted.

Dependence of Subsequent Weight on Birth Weight

In the first paper quoted the growth of children from 4 to 13 years was investigated, in the second that of children up to 3 years. The conclusions therefore apply to all ages of childhood up to 13 years. In amplified form the conclusions reached are as follows. 'Throughout childhood the average child who was a small baby at birth weighs considerably less than the average child who at birth was a large baby' . . . 'The same gradation of weight in relation to birth weight was shown in all the age groups studied' (Illingworth, 1950).

These conclusions are based upon a comparison of averages, as can be seen from Table 1, and also of ranges, without, however, considering the effect which the extent of the range must have upon the supposedly close correlation between birth weight and subsequent weight. The comparison in Table 1 is between the average subsequent weights of children who belong to different birth weight classes. Admittedly, there appears to be a tendency of subsequent weights at a given age to parallel the difference in birth weight, though no attempt is made to determine whether differences between the birth weight groups in that respect, which are sometimes very small, are really significant.

TABLE 1

RELATION OF BIRTH WEIGHT TO AVERAGE SUBSEQUENT WEIGHT (ILLINGWORTH, 1950)

	Group A (5 lb. 8 oz. or less)	Group B (7 lb. 2 oz.-7 lb. 6 oz.)	Group C† (8 lb. 8 oz.-9 lb. 7 oz.)	Group D (9 lb. 8 oz. or more)
	lb. oz.	lb. oz.	lb. oz.	lb. oz.
Boys				
Birth ..	4 14	7 4	8 13	9 15
1 year ..	20 12 (51)*	22 5 (36)	24 3 (104)	24 7 (44)
1 ,, ..	22 6 (18)	26 2 (23)	25 15 (46)	27 2 (22)
2 years..	24 3 (26)	26 8 (26)	28 15 (63)	29 1 (22)
2 ,, ..	28 0 (10)	—	30 14 (15)	30 11 (10)
3 ,, ..	28 9 (10)	—	33 10	(18)†
Girls				
Birth ..	5 0	7 4	8 13	9 14
1 year ..	19 11 (59)	21 13 (48)	22 8 (73)	23 3 (23)
1 ,, ..	21 15 (23)	24 13 (15)	24 10 (31)	25 4 9)
2 years..	24 12 (31)	27 0 (28)	26 15 (64)	29 9 (19)
3 ,, ..	28 1 (15)	—	32 8	(20)†

* The figures in parenthesis indicate the number of children in each group.

† Groups C and D are combined owing to smallness of numbers.

The point, however, which we wish to make here is that the comparison by means of averages, or ranges, is not satisfactory if it leaves out the adverse effect which the spread of subsequent weight around the mean, and the extent of overlap between birth weight categories in this respect, has upon the dependence of subsequent weight upon birth weight. To know this is essential because there is no such thing in nature as the 'average' child. This is a mathematical construction, and all we have before us is individual children and therefore individual weights. It is now just the subsequent weight of the individual child which is to be regarded in the light of its dependence upon the birth weight. If

one wishes to allay a mother's worry about her child being underweight for its age, by going back to the child's low birth weight as a sufficient explanation, then it is clearly not the average but the individual child one is concerned with, and the probable deviation of the individual child's weight from what is expected for the average child must not be forgotten.

The correct method for determining the dependence of subsequent weight upon birth weight is that of correlation analysis. Such an analysis was carried out for 3-year-old children by Lowe and Gibson (1953). The authors arrived at a correlation coefficient of ·49 for males and ·50 for females. The meaning of the correlation is this. It gives an overall idea of how much the variation of one variable is due to the variation in the other. In our case, it means how much of the variation in the subsequent weight, that is at 3 years of age, is due to the variation in the weight at birth. However, it is not the correlation coefficient but its square which determines the overlap in the number of small causes which produce the dependence in question. When both variables, say x and y, are assumed to be built up of simple elements of equal variability, it can be proved mathematically (Ezekiel, 1941) that r^2, the square of the correlation coefficient, means that proportion of the elements in y which is also present in x. For that reason, in cases where the dependent variable is known to be causally related to the independent variable, r^2 is to be regarded as the coefficient of determination. To show the meaning of r^2 in diagrammatic form (Fig. 1) let us assume that the area of each of the two circles represents the elements which go into the make-up of the variability of birth weights and subsequent weight. Their overlap then represents r^2.

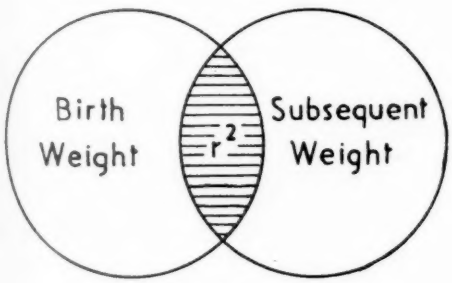

DIAGRAM 1

The square of the correlation coefficient, r^2, represents the overlap of small causes which determine birth weight and subsequent weight

It may be said to measure the percentage to which the variance in y is determined by x. Thus, in the given case, of the many causes which go into the make-up that determine subsequent weight, only $r^2 = \cdot 25$ or $\frac{1}{4}$, is common to both variables (weights). That shows that the dependence is really a rather restricted, if not a weak, one. These conclusions are confirmed in a study on children's weights (Bayley and Davis, 1935) where, in a very careful study of growth changes in 61 children, the author arrived at a correlation coefficient of ·40 between the series of birth weight and weight at 3 years of age. Since the random error of $r = \cdot 40$ is, in a sample of 61 individuals, approximately 0·11, this result is in good agreement with that reached by Lowe and Gibson, and we may, therefore, regard the range of the squares of r, viz. $\frac{1}{4}$ to $\frac{1}{8}$ approximately, as a good estimate of the intensity of dependence between birth weight and the weight at three years. This means that from 75% to 83% of the variation of body weight at 3 years is determined by factors other than birth weight.

Bayley and Davis also remark about the comparatively weak connexion between birth weight and weight at 3 years, which, according to them, is fourth in rank of the relations studied, viz., head circumference, length, stem-length (with $r = \cdot 72$, ·68 and ·59 respectively). I have left out in this assessment the reduction which the correlation coefficient would have to suffer on account of its being obtained only from a sample and not from the population itself, but even so it shows to what a great extent the fundamental statement at the beginning of this paper must be qualified as regards the intensity of connexion between birth weight and subsequent weight. And this must be taken into account whenever one wishes to explain a child's subsequent weight by reference to its birth weight. The error of estimate for an individual observation is a function of r^2; without going into mathematical detail, it may be sufficient to know that the smaller r^2, the greater the error.

Supposed Constant Relationship between Birth and Subsequent Weights

The relationship between birth weight and subsequent weight was taken to be constant at all ages studied, that is, from 1 to 13 years, but mere inspection of the numerical tables (Table 1) shows the relationship as anything but constant. As is only to be expected, it diminishes with increasing age and it is quite clear why this must be so. In the earliest stages of life the body weight will exceed the birth weight only by a small amount and therefore differences in the latter will be of paramount importance in the body weight at these early stages of life. The more, on the other hand, that weight

increases with age, the less important must the birth weight be as a constituent of the total weight, because it becomes relatively smaller and smaller compared with additional weight since birth. These conditions are fully confirmed by obtaining correlation coefficients for subsequent stages of life.

From a survey of the growth of babies in Bristol during 1951 (Table 2), correlation coefficients were calculated between birth weight and the weight at 13 weeks, and furthermore, between birth weight and the weight at 26 weeks.

TABLE 2

AVERAGE WEIGHT OF BRISTOL CHILDREN BORN IN 1951 AT 13 AND 26 WEEKS ACCORDING TO BIRTH WEIGHT CLASSES

Birth Weight in lb.	Average Weight at 13 Weeks (lb. oz.)	Average Weight at 26 weeks (lb. oz.)
– 4·5	—	14·28 (1)
– 5·0	9·59 (1)*	13·32 (2)
– 5·5	11·11 (2)	17·25 (2)
– 6·0	11·50 (15)	16·31 (9)
– 6·5	11·39 (16)	16·13 (13)
– 7·0	11·93 (25)	17·05 (14)
– 7·5	12·46 (40)	16·95 (38)
– 8·0	13·25 (36)	17·12 (26)
– 8·5	13·29 (26)	18·04 (23)
– 9·0	13·28 (19)	18·89 (15)
– 9·5	14·28 (9)	19·03 (9)
–10·0	14·34 (2)	18·42 (4)
–10·5	15·72 (2)	18·88 (4)

* The figures in parenthesis give the numbers of children in each weight class.

The correlation coefficients were ·56 and ·44 respectively. These results are in agreement with the considerations at the beginning of this section. The decrease of the correlation coefficient with age of the child is confirmed by Bayley and Davis who obtain a markedly higher correlation coefficient after 1 year of age than the figure they give in their paper for the relation at 3 years of age. Thus the dependence, such as it is, is not constant through childhood, but decreases systematically with age.

Hypothetical Influence of Birth Weight upon Weight Gain

The hypothesis of birth weight standing in an important relationship to subsequent weight does not imply, as might be thought, a continuous influence of the former upon the way a child grows. If correlation analysis is applied to such data almost the opposite is seen to be true. Lowe and Gibson have calculated the regression equation between birth weight (x) and weight at 3 years of age (y) as (roughly) $y=25\cdot3+x$ for males and $y=24\cdot6+x$ for females. This means in words that the excess of a child's weight over a constant weight gain roughly of 25 lb. is represented by the birth weight. This implies that no matter what the birth weight, a child will, on an average, gain 25 lb. in three years. If that is true, then clearly growth in terms of weight gain since birth is independent of birth weight. In other words the latter has no influence upon the way in which a child grows.

Although Lowe and Gibson's findings of a constant weight gain independent of birth weight are supported by another investigator (Parfit, 1951), yet the matter of growth seems too complex for us to abide completely by these conclusions unless they were supported by more material. It is very difficult to imagine that the factors which make for weight act in such a way as to make the weight increase constant for all children irrespective of their birth weight.

The investigation on babies' weights in Bristol mentioned above does, at any rate, not fully bear out such an assumption (Table 3).

If the weights at 3 and 6 months are examined, and the children divided into two groups, that is with birth weight up to 7 lb. and those with birth weight higher than 7 lb., it is found that the average weight increase is for the first group 5·34 lb. and for the second group 5·15 lb. Thus the increase seems to be in inverse relation to the average birth weight. At 6 months of age we find for the first group, that is for the lighter children, the average increase to be 10·02 lb. and for the heavier children 9·50 lb.

TABLE 3

AVERAGE WEIGHT GAIN OF BRISTOL CHILDREN BORN IN 1951 AT 13 AND 26 WEEKS ACCORDING TO BIRTH % WEIGHT CLASSES

Weight at Birth (lb. oz.)	Average Weight Gain at 13 Weeks (lb. oz.)	Average Weight Gain at 26 Weeks (lb. oz.)
		9·84 (1)
5·0	4·90 (1)*	8·63 (2)
5·0– 5·5	5·84 (2)	12·03 (2)
5·5– 6·0	5·73 (15)	10·65 (9)
6·0– 6·5	5·19 (16)	9·90 (13)
6·5– 7·0	5·25 (25)	10·35 (14)
7·0– 7·5	5·29 (40)	9·80 (38)
7·5– 8·0	5·24 (36)	9·47 (26)
8·0– 8·5	5·17 (26)	9·95 (23)
8·5– 9·0	4·69 (19)	9·98 (15)
9·0– 9·5	5·16 (9)	9·94 (9)
9·5–10·0	4·72 (2)	8·83 (4)
10·0–10·5	5·19 (2)	8·81 (4)

* No. of children in each group.

The weight gain is thus again in inverse relation to the average birth weight. These results may be tabulated as follows.

AVERAGE WEIGHT GAIN OF CHILDREN BORN IN BRISTOL IN 1951 AT 13 AND 26 WEEKS ACCORDING TO TWO BIRTH WEIGHT CLASSES

Birth Weight	13 Weeks	26 Weeks
<7 lb.	5·34 lb.	10·02 lb.
>7 lb.	5·15 lb.	9·50 lb.

Without wishing to decide whether such reversal is sympathetic and must be expected, we may look upon it as an indication that the hypothesis of the weight increase as being entirely independent of the birth weight may not be correct, and that the influence of birth weight upon weight gain may even be the reverse of what the original hypothesis implied it to be. Another point which makes us suspect the hypothesis is the curious reversal which Lowe and Gibson have observed as regards the correlation between birth weight and birth order, and between subsequent weight and birth order, the first giving a positive correlation and the latter a negative correlation. It is clear that had the increase been the same throughout, the correlation would have remained positive. If, on the other hand, the increase had a systematic inverse trend with birth weight, then we should expect a reversal of this kind. However this may be, it looks as if the view of a complete independence of weight gain and birth weight was an over-simplification of the matter and that probably the relation, whatever it may be, changes with age.

Summary

(1) Birth weight exerts a definite, but rather restricted, influence upon subsequent weight. At 3 years of age it could be assessed as accounting for not more than 25% of the variation in subsequent weight.

(2) The relation between birth weight and subsequent weight is not constant but decreases systematically with the age of the child.

(3) The relation under (1) implies, as far as it goes, that 'growth', in terms of weight gain, is independent of the birth weight. This, however, is shown to be an over-simplification of the actual relationship.

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HYPERAMINO-ACIDURIA IN LIGNAC-FANCONI DISEASE, IN GALACTOSAEMIA AND IN AN OBSCURE SYNDROME

BY

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The observation of various conditions with increased excretion of amino-acids in the urine has given rise to problems of differential diagnosis, many of which are still unsolved. This paper will compare and contrast three different diseases with increased amino-acid excretion. It is based on the description of the following cases; the first an example of Lignac-Fanconi disease, the second an infant suffering from galactosaemia, and the third a child with an obscure syndrome.

The detection of disturbances of amino-acid metabolism in a variety of diseases has been made possible since Consden, Gordon and Martin (1944) introduced paper chromatography. Dent (1947, 1948) first applied this new technique to the study of the amino-acid composition of biological fluids. It soon became clear that paper chromatography is a useful semi-quantitative method for investigating the urine for amino-acids and other substances, e.g., sugars.

Research of this kind has been systematically carried out in Great Britain by Dent (1949, 1950), Woolf (1951) and Bickel (1950, 1952). These and other workers have used paper chromatography to study hyperamino-aciduria in newborn and premature infants (Souchon, 1952), cystine-lysinuria (Dent and Rose, 1951), Lignac-Fanconi disease (Bickel, Smallwood, Smellie, Baar and Hickmans, 1953), phenylpyruvic oligophrenia (Woolf and Vulliamy, 1951; Meister, 1951), liver disease (Dent and Walshe, 1951; Walshe, 1951), idiopathic steatorrhoea and coeliac disease (Bickel, 1952), hepatolenticular degeneration (Uzman and Denny-Brown, 1948; de Verdier, 1950), galactosaemia (Holzel, Komrower and Wilson, 1952; Bickel and Hickmans, 1952), the Fanconi syndrome of adults (Dent, 1948; Milne, Stanbury and Thomson, 1952) and other diseases.

Lignac-Fanconi Disease

Case 1. The boy was the only child of healthy parents. Nothing abnormal was noticed until he was 10 months old, when he began vomiting intermittently. At 13 months the vomiting became more frequent, his appetite failed and he lost weight. He developed severe thirst with polyuria.

On admission (aged 15 months) he was a small, thin, pale child with fair hair and sunken eyes (Fig. 1) and weighed 18 lb. 2 oz. He appeared ill and dehydrated, and was very fretful. Signs of rickets, such as a large fontanelle, slight bossing of the forehead and broadening of the epiphyses were noted. His muscles were hypotonic. The liver and spleen were not palpable. A radiograph of the wrists confirmed active rickets.

FINDINGS IN THE BLOOD AND URINE†. The blood chemistry is shown in Table 1. Haemoglobin was 11·5 g. %, and leucocytes 16,600 per c.mm. (polymorphs 34%, lymphocytes 66%). A reducing substance was found in the urine; it was identified by chromatography as glucose (Fig. 2), but the blood sugar levels were normal. An oral glucose tolerance test with 6·5 g. glucose gave

FIG. 1.—Two children with hyperamino-aciduria and a healthy child. From left to right, Case 3 aged 5 years, healthy child aged 5½ years, Case 1 aged 5½ years.

* In receipt of a grant from the Medical Research Council.

† For biochemical and chromatographic methods see Bickel and Hickmans (1953).

half-hourly blood sugars of 138 (fasting) to 164, 170, 186, 120, 138 mg. per 100 ml.

The 24-hour urine volume, measured at the age of 16 and 17 months, was 1,010 ml. and 1,430 ml. (average normal for a child of 1 year being 300 to 600 ml.). The specific gravity was 1,002-1,010, and albumin 10 mg. %. The centrifuge deposit showed an occasional pus cell, but no red cells or casts. The reaction of the urine varied, but was usually acid. The ammonia coefficient

$$\frac{(\text{ammonia nitrogen} \times 100)}{\text{total nitrogen}}$$

was slightly raised to 5·2-6·5% (normal 2%-4%).

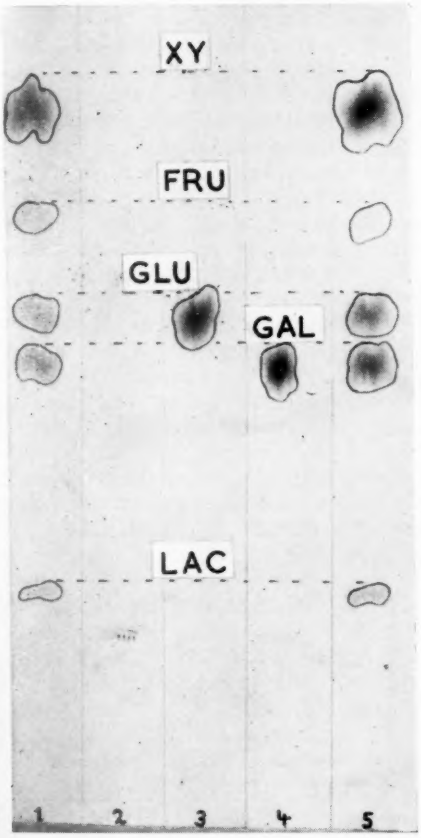

FIG. 2.—One-dimensional sugar chromatogram with urines of Case 3 (column No. 2). Case 1 (column No. 3), and Case 2 (column No. 4), showing glycosuria in Case 1 and galactosuria in Case 2. Urine volume in all cases 100μl. For purposes of comparison pure lactose, galactose, glucose, fructose and xylose were run in the two outer columns.

INVESTIGATIONS OF AMINO-ACID METABOLISM. At the age of 16 months cystine crystals were found in the urinary deposit. Dr. C. E. Dent, University College Hospital, London, then demonstrated an excessive urinary excretion of some 10 to 15 amino-acids by means of paper chromatography, and this was confirmed by us in many subsequent specimens (Fig. 3).

The amino-acid nitrogen coefficient in the urine

$$\frac{(\text{amino-acid nitrogen} \times 100)}{\text{total nitrogen}}$$

was raised to 3·6% (normal up to 2%).

The amino-acid content of the plasma was tested by paper chromatography and the colour intensity of various amino-acids was found to be 50% or more above the normal range. The amino-acid pattern closely resembled that in the patient's urine. Paper chromatography is, however, a semi-quantitative method unsuitable for the assessment of slight changes of the amino-acid concentration in plasma.

The clinical and biochemical features of Case 1, especially the pattern of the hyperamino-aciduria and the glycosuria, suggested the diagnosis of Lignac-Fanconi disease. A search for cystine crystals in the eyes by slit-lamp revealed a typical distribution of masses of crystals in the cornea and conjunctiva. Bone-marrow films likewise showed cystine deposits, the crystallographic characteristics of which were recently discussed in detail by Baar and Bickel (1952).

The patient's mental development has been above that of the average child, but physical development has been much retarded. He is now 5½ years old and his height is 35 in. and weight 25½ lb. (Average normals for this age stand 43 in. high and weigh 43 lb.) At 2½ years old alkali treatment was started (sodium citrate 100, citric acid 140, water to 1,000 ml., 10 ml. five times daily by mouth), and also 'calciferol' (50,000 units, later reduced to 15,000 units, daily by mouth). During the following

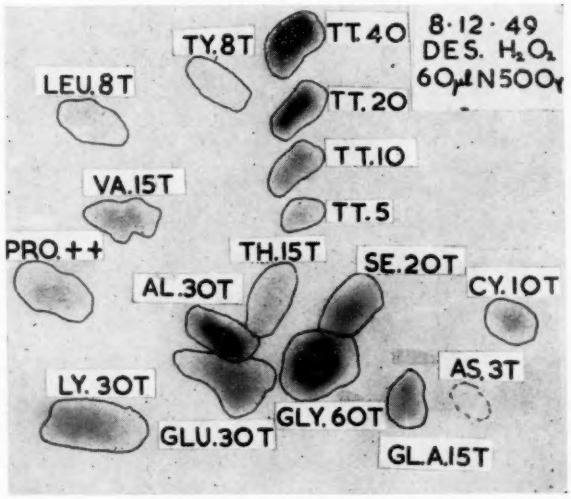

FIG. 3.—Two-dimensional amino-acid chromatogram with urine of the patient with Lignac-Fanconi disease (Case 1). For all amino-acid chromatograms a urine volume≡500γ N_2 was taken.

AL.=alanine; AS.=aspartic acid; CY.=cystine as cysteic acid; GL. A.=glutamic acid; GLU.=glutamine; GLY.=glycine; LEU.=leucine + isoleucine; LY.=lysine; PRO.=proline; SE.=serine; TH.=threonine; TY.=tyrosine; VA.=valine. TT.5, 10 etc.=5γ, 10γ etc. test taurine, added to the chromatogram before the run. Figures beside amino-acids indicate colour intensity and size of spots as compared with taurine test spots (e.g., 10T=colour and size of spot equal to 10γ taurine).

year on this treatment the condition greatly improved, the rickets healed, his appetite increased and the vomiting practically ceased. The child grew 2 in. and gained 3 lb. 4 oz. in weight. He continued to suffer from abnormal thirst and polyuria, but no further metabolic crises have been observed.

Galactosaemia

Case 2. A baby girl, aged 10 days, was admitted with vomiting and slight jaundice. She was a full-term baby from a normal delivery, weighing 8 lb. at birth. She seemed normal for the first week of life. Slight jaundice then appeared, which fluctuated in intensity. She began vomiting when 9 days old. The mother maintained that the child's symptoms were similar to those shown by her previous child, who died in 1948, aged 11 weeks. This sibling had had cirrhosis of the liver and a cataract in the right eye.

On admission the baby was pale and slightly jaundiced, weighing 6 lb. 11 oz. The liver was greatly enlarged, and the lower edge could be palpated 3½ in. below the right costal margin. The umbilicus showed evidence of recent haemorrhage and sepsis which was at first thought to account for her symptoms. The eyes showed no sign of cataracts. The urine contained protein and a trace of sugar; bilirubin and urobilin were also present. After admission vomiting continued, and dehydration was corrected by parenteral fluids.

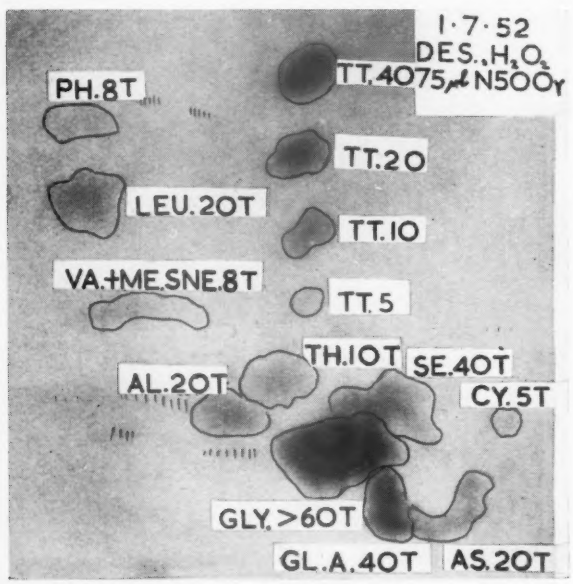

FIG. 4.—Two-dimensional amino-acid chromatogram with urine of a case of galactosaemia. ME.SNE.=methionine as methionine sulphone; PH.=phenylalanine.

FINDINGS IN BLOOD AND URINE. At the age of 5 weeks the serum bilirubin was 0·66 mg. per 100 ml.; thymol turbidity 4·5 units; alkaline phosphatase 17 Kay units, albumin 4·0, globulin 5·0 g. %. The urine was found to contain 1·8% of a reducing substance which was identified by paper chromatography as galactose (Fig. 2). A galactose tolerance test provided further support for the diagnosis of galactosaemia. The fasting blood galactose was 14 mg. %, and after 5·25 g. of galactose by mouth (1·75 g./kg.) rose to 254 mg. % in 2 hours.

CHROMATOGRAPHIC INVESTIGATIONS. After three months on a galactose-free diet the urine was again tested by sugar chromatography but no sugar was detected. Amino-acid chromatograms were then carried out for the first time and were normal. Five months later the child was put for one day on a diet containing 600 ml. milk and galactose reappeared in the urine, but the amino-acid excretion remained normal. In two cases of galactosaemia studied before the elimination of lactose from the diet paper chromatography revealed hyperamino-aciduria (Fig. 4) which was also described in two patients by Holzel *et al.* (1952).

At the age of 5 weeks milk feeds were stopped, and a lactose-free regime was instituted. This was followed by marked improvement, reducing substances disappeared from the urine and the enlarged liver slowly returned to normal size. Solid food was gradually introduced into the diet at the normal age, and the child made normal progress with no evidence of mental retardation or the development of cataracts. At 11 months old there was no galactose in the fasting blood specimen, but after 18 g. of galactose by mouth, the half-hourly blood galactose levels were 50-117-167-234 mg. %. There was no hyperamino-aciduria during the test. At 19 months the child's height is now 28½ in., and her weight is 21 lb. 12 oz. The galactose intolerance, however, remains unchanged.

Hyperamino-aciduria in an Obscure Syndrome

Case 3. The boy is the second child in a healthy family, and was delivered by forceps (birth weight 9 lb.). At 4 months he was noticed to have bilateral cataracts. From the second year onwards it became apparent that his mental and physical development was almost static. The joints could be bent like an acrobat's, and he developed senseless jerking movements of the limbs with frequent grimacing. His appetite was poor and he was often constipated, but there was no vomiting.

On admission (aged 4 years 5 months) he was dwarfed (34½ in., normal 39 in.) and weighed 27½ lb. (Fig. 1). He looked pale and flabby, was very hypotonic, and displayed remarkable mannerisms in which he rapidly jerked his hyperflexible limbs and waggled his fingers in front of his eyes. He was almost blind, though he could distinguish light and darkness. There was considerable enophthalmos due to lack of periocular fat, and a coarse, searching nystagmus. The abdomen was protuberant, there was divarication of the recti and an umbilical hernia. Rickets was evident from frontal bossing, a slight rosary, enlarged wrists and knock knees. Radiographs showed gross active rickets, osteoporosis, and the suggestion of a pseudo-fracture of the left femur. Carpal ossification was equivalent to that of a boy of

2 years. Ophthalmological examination revealed bilateral capsulolenticular cataracts.

FINDINGS IN BLOOD AND URINE. Normal values for red blood cells, haemoglobin, leucocytes, the differential count, prothrombin time and platelets were obtained. A differential count of the bone marrow showed low cellularity with an increase of immature white cells; no cystine crystals were seen in sections fixed in alcohol.

The blood chemistry is given in Table 1.

The cholesterol and bilirubin levels and thymol turbidity were normal. The 24-hour urine volume was 300 to 600 ml. The urine contained 40-90 mg. % protein. Benedict's test and chromatography were negative for sugar (Fig. 2) except in two specimens, where traces of glucose and galactose were detected. The centrifuged urine deposit was often found to contain some granular casts and tyrosine crystals. The urine *p*H varied between 7·8 and 5·7. Bicarbonate excretion was 2·3 (*p*H 6·6) and 0·8 mEq./l. (*p*H 5·7). The ammonia coefficient was 4%, 10% and 10%.

GALACTOSE TOLERANCE TESTS. These were performed because of the clinical resemblance between this patient and cases with galactosaemia. (*a*) Within four hours after ingestion of 30 g. galactose, only 0·3 mg. and, in a repeat, 0·5 mg. galactose, were excreted in the urine. (*b*) Blood galactose levels were estimated after ingestion of 20 g. galactose. The half-hourly blood galactose levels were nil (fasting) to 17, 86, 134, 17 mg. per 100 ml. Repeating the test the levels were nil to 17, 84, 134, 17 mg. per 100 ml. According to Peters and Van Slyke (1946), the tests under (*a*) were normal, but the blood tolerance curve of test (*b*) was somewhat high and prolonged.

HIPPURIC ACID TEST. Only 37% of 3 g. ingested sodium benzoate was recovered in the urine as hippuric acid within four hours (normal above 50%).

LIVER BIOPSY. The liver architecture was normal. Glycogen was abundant, though not excessive in all liver cells. There was no suggestion of glycogen storage

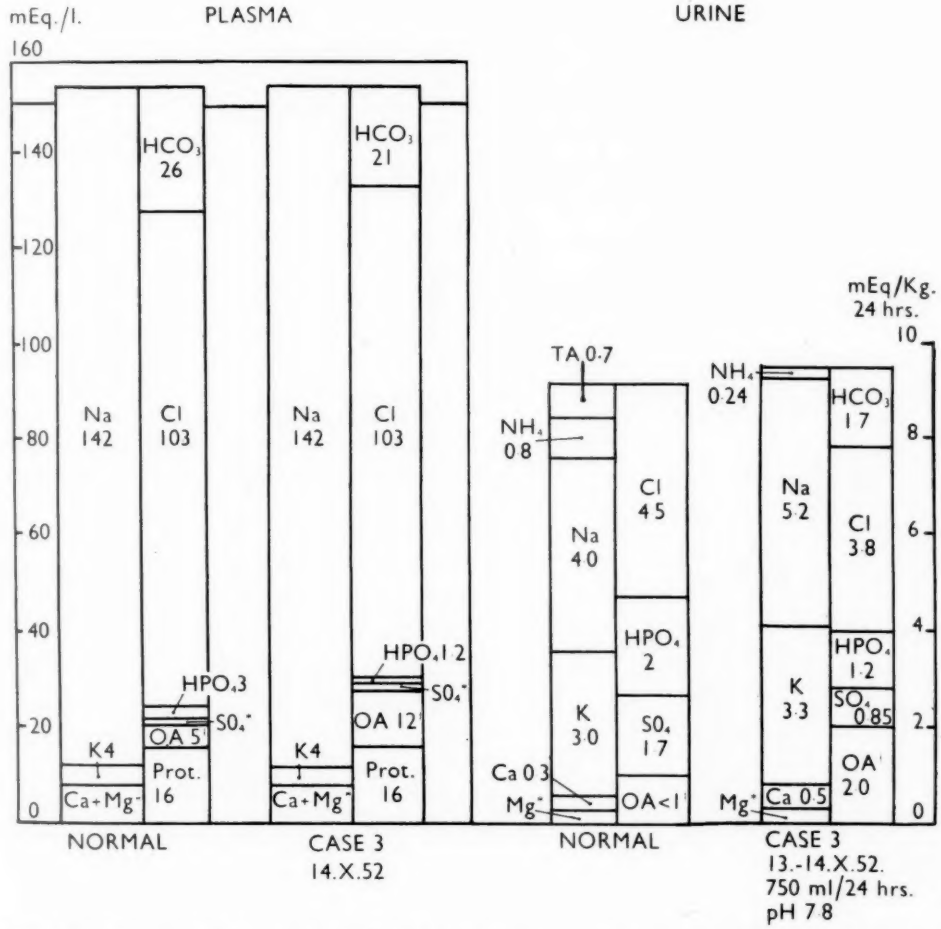

FIG. 5.—Electrolytes in plasma (left) and urine (right) of Case 3 as compared with average normal values for plasma and urine. OA = organic acids, estimated by subtracting the other anions from the total bases.

disease. No cystine crystals were found. Some nuclei contained periodic-acid-Schiff-positive material, but similar changes have also been found in other conditions and probably represent nuclear glycogen deposits despite their resistance to short salivary digestion.

KIDNEY FUNCTION TESTS. The average urea clearance corrected for surface area was 91%. Urography showed normal diodone concentration and no structural abnormalities of renal pelves or ureters. In a water concentration test the specific gravity of the urine rose to 1,024 after 16 hours' deprivation of water.

CALCIUM-PHOSPHORUS BALANCES. The results were essentially normal, but they were probably influenced by a single dose of 100,000 units vitamin D before admission, three weeks before the balance.

ELECTROLYTIC FINDINGS. In the plasma there were hypophosphataemia and a moderately decreased bicarbonate level (Fig. 5). The plasma organic acids, estimated by difference between total bases and the measured anions, were 12 mEq./l. which is at the upper limit of normal. The 24-hour urine specimen was alkaline (*p*H 7·68), with a high bicarbonate and low ammonia content. The excretion of phosphate and sulphate was small, that of organic acids (estimated as in plasma but taking titratable acidity into account) was raised to 2·0 mEq./kg./24 hours. The urine was collected under toluene with thymol crystals added.

INVESTIGATIONS OF AMINO-ACID METABOLISM. Chromatograms of numerous urine specimens showed a constant and considerable hyperamino-aciduria (Fig. 6). The total colour intensity of the chromatograms was often five times that of normal urine. The amino-acid nitrogen coefficient was 4·5%.

The sum of the glutamine and glutamic acid in the plasma was raised to 13·8 and 14·0 mg. per 100 ml. (normal 7-10 mg. per 100 ml.).* The daily urine excretion of these amino-acids was 535 mg. (normal up to 100 mg. per day). Chromatographic investigation of two plasma specimens gave no conclusive evidence of an increased amino-acid concentration, though the level of various amino-acids, especially of cystine, lysine, threonine, tyrosine and phenylalanine seemed to be above the upper limit of normal.

TABLE 1
BIOCHEMICAL FINDINGS IN CASES 1 AND 3

Biochemical Finding	Case 1 Range	Case 3 Range	Normal Range
Serum calcium ..	10·3 –10·8	9·1–11·6*	9·0–11·5 mg. %
Serum phosphorus ..	1·8 – 5·2*	2·1–2·8	4·5– 5·5 mg. %
Serum alkali phosphatase ..	30·2*–50·0	40·4–46·2	8–15 Kay units
CO_2-combining power	13·5 –27·9†	18·8–22·1†	24–30 mEq./l.
Blood urea ..	16·5 –75·0‡	22·6–36·1	20–40 mg. %
Serum albumin ..	4·6		4·5 g. %
Serum globulin ..	2·6		2–2·5 g. %
Plasma potassium ..	3·3	3·8–4·4	3·8–5·0 mEq./l.
Plasma sodium ..		137	137–145 mEq./l.
Plasma chlorides ..		103	96–110 mEq./l.
Fasting blood sugar	84 –138	80	75–110 mg. %

* During massive vitamin-D therapy.
† During alkali therapy.
‡ During dehydration.

Treatment with 8 g. sodium citrate and 5,000 units 'calciferol' daily did not produce marked improvement, and the rickets remained active. Large doses of 50,000 units of 'calciferol' daily were not well tolerated and produced a moderate elevation of the serum calcium level to 11·6 mg. per 100 ml. A lactose-free diet also failed to bring about any improvement in the clinical or biochemical picture.

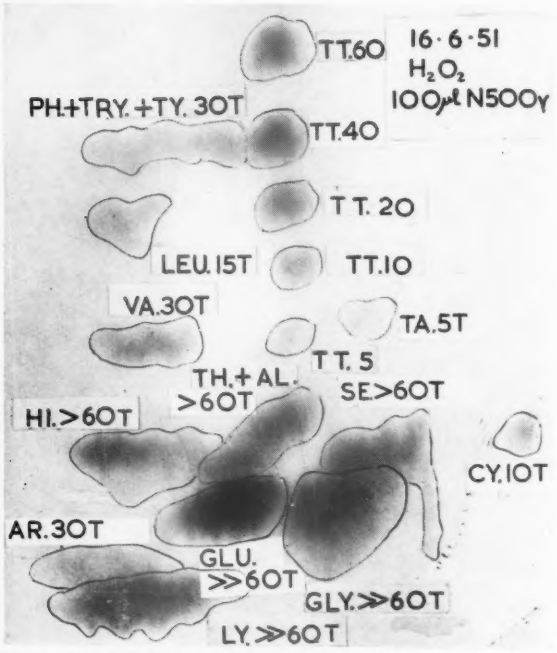

FIG. 6.—Two-dimensional amino-acid chromatogram with urine of the patient with the obscure syndrome (Case 3). AR.=arginine; HI.=histidine; TA.=taurine; TRY.=tryptophane.

Discussion

Case 3 shows a peculiar syndrome characterized by bilateral cataracts, enophthalmos, hypophosphataemic rickets and dwarfing. The patient is backward in his mental and physical development, and shows severe muscular hypotonia. In the blood the CO_2-combining power is reduced, and in the urine there is slight albuminuria and a strong hyperamino-aciduria. The special interest of this syndrome lies in its partial resemblance to Lignac-Fanconi disease and galactosaemia, inborn errors of amino-acid and galactose metabolism.

Lignac-Fanconi Disease. This name is applied here to a condition which has been described under various names, such as cystine storage disease or Lignac's disease, nephrotic-glycosuric dwarfism with

* We are indebted to Professor H. A. Krebs for carrying out this estimation.

hypophosphataemic rickets, de Toni-Debré-Fanconi syndrome, cystine rickets, amino-acid diabetes, etc. It seems doubtful whether all these cases correspond to one clinical entity. The name 'Fanconi's syndrome' in particular has been applied rather indiscriminately to conditions characterized by hypophosphataemic rickets or osteomalacia, hyperamino-aciduria, perhaps with glycosuria, acidaemia, with or without dwarfing, in children and adults. The one term may thus conceal quite different diseases, for which a common name is misleading, as it invites generalizations. If, however, cystine storage is regarded as an essential feature of the disease, then such cases form a well defined clinical entity which for purposes of clear distinction we propose to call Lignac-Fanconi disease (Lignac, 1924; Fanconi, 1936). It is our contention that in many cases of Fanconi's syndrome reported in the literature, cystine storage has been overlooked during life and even at necropsy. Slit-lamp investigations for cystine crystals in the cornea and conjunctiva are difficult in young children, and cystine crystals in bone-marrow smears are often scanty and easily dissolved in acid stains or water.

Case 1 represents a typical example of Lignac-Fanconi disease as we have observed it in 17 further patients (Bickel *et al.*, 1953). In this case anorexia, vomiting, polyuria and dehydration were the presenting symptoms, beginning characteristically in the second six months of life. The finding of glycosuria at first suggested the diagnosis of diabetes but the blood sugar level was normal. The child was dwarfed, and this became more striking as he grew older, though a small measure of growth was achieved by treatment with sodium citrate-citric acid solutions and massive doses of 'calciferol'. This treatment cured the rickets, produced a remarkable general improvement and led to the cessation of the hyperamino-aciduria*. Although the hyperamino-aciduria varied considerably from day to day it was always of a pattern characteristic of the disease. No quantitative amino-acid blood tests were carried out, but in six other cases investigations by microbiological assay by Dr. K. Schreier, and by the glutaminase method by Professor H. A. Krebs, showed a raised plasma level of various amino-acids (Bickel and Hickmans, 1953; Philpott, Harvey and Finch, 1953). The demonstration of cystine storage in eyes and bone-marrow established the diagnosis, and was a regular feature of all our other cases. Hypopotassaemia is another important biochemical finding in Lignac-Fanconi disease, though it may not be observed in the presence of dehydration, a common occurrence in such patients.

Cases 1 and 3 showed many points of resemblance, but at the same time certain important differences. dwarfing, rickets with a low serum phosphorus and high phosphatase, hyperamino-aciduria and reduced CO_2-combining power, were seen in both. On the other hand, cystine storage, polyuria and polydipsia, which were marked in Case 1, were absent in Case 3. Case 3 also differed from the case of Lignac-Fanconi disease in being mentally retarded and suffering from enophthalmos and cataracts. Finally, the relative amounts of various amino-acids in the urine, such as the strong excretion of histidine, tyrosine and phenylalanine, differentiated Case 3 from Case 1. Case 3 could not thus be classified under the diagnosis of Lignac-Fanconi disease. The retarded mental development and bilateral cataracts drew attention to another possibility, galactosaemia, particularly as a trace of galactose was found in the sugar chromatogram of the urine on two occasions.

Galactosaemia. When milk feeds were started in the neonatal period Case 2 showed the characteristic features of this condition, i.e., transient jaundice, hepatomegaly, albuminuria and galactosuria. Galactose tolerance tests and the improvement on the lactose-free formula confirmed the diagnosis. The sibling who died untreated four years previously had cataracts and cirrhosis of the liver. Older untreated cases are usually mentally retarded. The assessment of the most important diagnostic feature, galactosuria, may prove difficult. A patient has been described by Townsend, Mason and Strong (1951) and another by Bray, Isaac and Watkins (1952) who, though proved or probable cases of galactosaemia, could at the age of 7 years tolerate a milk intake of 200 and 500 ml. respectively without showing galactosuria. On the other hand, galactosuria has been observed in other conditions, such as liver cirrhosis, liver atrophy, and in newborn infants (Rapoport, 1950). Thus intolerance of galactose after a test dose may simply be a sign of impaired liver function. Despite these limitations, the demonstration of galactosuria and impaired galactose tolerance are still important factors in establishing the diagnosis. Sugar chromatography is a specific, sensitive, and relatively simple method of demonstrating galactose in the urine, especially when it occurs only in traces or together with other sugars.

Another biochemical abnormality found in galactosaemia is hyperamino-aciduria, which has been observed independently by Holzel *et al.* (1952)

* A recurrence of the hyperamino-aciduria and rickets has recently been observed in a boy with Lignac-Fanconi disease whose 'calciferol' treatment had been stopped but who was satisfactorily alkalized. This suggests that vitamin D therapy, not alkalization, leads to the cessation of the hyperamino-aciduria.

and by Bickel and Hickmans (1952). A striking feature of the hyperamino-aciduria in both of Holzel's patients was its disappearance with the omission of galactose from the diet and reappearance when galactose was again given. Two of our patients, however, continued to show a definite though reduced hyperamino-aciduria for months after the institution of a galactose-free diet. This discrepancy may depend on the extent to which the liver or kidney damage leading to the hyperamino-aciduria remains reversible. Case 2 in this paper was diagnosed and treated exceptionally early, and showed no hyperamino-aciduria even during galactose ingestion. We do not know if there is a characteristic amino-acid pattern in galactosaemia, as there is in Lignac-Fanconi disease.

Despite cataracts and retarded development, there seems sufficient evidence to exclude the diagnosis of galactosaemia in Case 3. The liver was not markedly enlarged, and its normal architecture in the biopsy contrasted with the cirrhotic and necrotic changes found in galactosaemia. The results of the galactose tolerance and hippuric acid tests point to some liver dysfunction, but the galactose intolerance does not seem severe enough to justify the assumption of an inborn error of the galactose metabolism. There was no clear-cut galactosuria in the chromatograms, and a galactose-free diet did not prove beneficial.

There was a striking resemblance of Case 3 to three patients recently described by Lowe, Terrey and MacLachlan (1952). These children showed mental retardation, flabby musculature with an abundance of subcutaneous fat, a peculiar, high-pitched cry, intermittent fever, glaucoma and cataracts. Active rickets was demonstrated in two of them, one of whom suffered from multiple fractures. Biochemical features included hyperamino-aciduria, organic-aciduria, reduced CO_2-combining power and, in two cases, slight glycosuria. The ammonia production following the administration of ammonium chloride was decreased.

There are, however, certain differences between Lowe's patients and Case 3. Glaucoma, the peculiar cry and intermittent fever were not features of our patient, and his ammonia production seemed normal. though this was not estimated during ammonium chloride feeding. The pattern of the hyperamino-aciduria in Lowe's cases was similar to that in Case 3, though our patient excreted in addition arginine, tyrosine and phenylalanine. The sum of glutamine and glutamic acid in the plasma of Case 3 provides evidence that the blood levels of at least these amino-acids are raised and that the hyperamino-aciduria is not entirely renal in origin, as suggested in Lowe's cases.

Lowe defined his patients' disease as 'organic-aciduria', as their organic acid excretion was too high to be accounted for solely by amino-acid increase. Our Case 3 showed an increase of the organic acid excretion to 2·0 mEq./kg./24 hrs. (normal less than 1 mEq./kg./24 hrs.) when estimated by the indirect method of subtracting the known anions from total bases. According to Dent (1953) and Linder, Bull and Grayce (1949), this is at present the only practicable method in the presence of hyperamino-aciduria, as the amino-acids interfere with the end-point determination of Van Slyke and Palmer's titration method used by Lowe. The moderate increase of organic acids in Case 3 is probably satisfactorily explained by the approximately threefold increase of the amino-acid content in the chromatogram of this urine specimen, which in terms of milliequivalents would amount to about 1·6 mEq./kg./24 hrs.

In conclusion, though not showing all the features of the syndrome described by Lowe, Terrey and MacLachlan, the disease of Case 3 certainly bears a closer resemblance to that syndrome than to either Lignac-Fanconi disease or galactosaemia. The differences mentioned above may be due not to a fundamentally different disorder but to individual variations in the features of the disease.

Summary

Various diseases with hyperamino-aciduria are enumerated, some of which present difficulties in differential diagnosis. Representative cases of three such conditions, Lignac-Fanconi disease, galactosaemia and an obscure syndrome, are described in detail.

Lignac-Fanconi disease represents a clearly defined clinical entity if cystine storage is regarded as an essential feature of the condition. The hyperamino-aciduria is of a characteristic pattern involving the increase of some 10 to 20 amino-acids. Glycosuria may be minimal and traceable only by sugar chromatography.

For the diagnosis of galactosaemia the demonstration of galactosuria and galactose intolerance is fundamental, though not conclusive. The significance of the hyperamino-aciduria recently demonstrated in this disease is still unknown.

An obscure syndrome consisting of hyperamino-aciduria, mental and physical retardation, peculiar motility and mannerisms, cataracts, enophthalmos, hypophosphataemic rickets, muscular hypotonia, reduced CO_2-combining power of the blood and albuminuria is described in a $4\frac{1}{2}$-year-old boy. Despite certain similarities to Lignac-Fanconi disease

and galactosaemia both diagnoses were excluded. There was, however, a considerable resemblance to a syndrome recently described by Lowe, Terrey and MacLachlan, though an increase in the urine of organic acids other than amino-acids was not a feature of our case.

We are greatly indebted to Dr. A. J. McCall for his generous help, to Professor J. R. Squire for his constructive criticism, and to Dr. H. S. Baar and Dr. E. M. Hickmans for much good advice. Dr. Frances Braid gave us facilities for metabolic studies in Case 3 and Professor H. A. Krebs kindly carried out glutamine estimations in urine and plasma of the same patient. The nursing staff of the North Staffordshire Royal Infirmary and the Children's Hospital, Birmingham, showed great skill in nursing these difficult children. We are also grateful to Dr. F. Fletcher of Benger's Ltd. for supplying the lactose-free peptone for the treatment of the patient with galactosaemia.

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Addendum

Since this paper was written we have had the opportunity of studying the development of hyperamino-aciduria in Lignac-Fanconi disease and galactosaemia since birth. The baby with Lignac-Fanconi disease was perfectly healthy until the age of 5 months, when hyperamino-aciduria and glycosuria slowly developed together with certain typical symptoms, thirst, anorexia, dehydration and failure to gain weight. At the same time the first few cystine crystals appeared in the cornea and bone marrow, while a lymph-gland biopsy showed abundant crystals.

In a newborn infant with galactosaemia no hyperamino-aciduria was present on the third, fourth and fifth days of life, despite massive galactosuria. When re-examined at 3 months of age hyperamino-aciduria was found, together with a raised alpha-amino-nitrogen in the plasma of 8·8 and 8·3 mg. per 100 ml. (gasometric ninhydrin method). When the child was given a galactose-free diet the hyperamino-aciduria ceased and did not return during two subsequent galactose tolerance tests.

BIOCHEMICAL CHANGES AND OSTEOSCLEROSIS AFTER SULPHAMEZATHINE THERAPY IN IDIOPATHIC HYPERCALCAEMIA OF INFANCY

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In communications to the British Paediatric Association in 1952, Lightwood and Payne described a group of 10 infants between the ages of 3 and 7 months presenting with anorexia, vomiting, failure to thrive, constipation and sometimes polyuria and polydipsia. They had hypercalcaemia, azotaemia and normal alkali reserves and in two of them radiographs showed nephrocalcinosis. There was no obvious cause for the hypercalcaemia, such as hyperparathyroidism or hypervitaminosis D, so they regarded it as a new syndrome. Fanconi and Girardet (1952) and Schlesinger, Butler and Black (1952) described two cases with hypercalcaemia and bone changes similar to those described in this communication. In the case described by Fanconi and Girardet hyperphosphataemia was present and the calcium-phosphorus product considerably raised. Creery (1953) described a case of hypercalcaemia in infancy and this child had osteosclerosis and at times a very high serum calcium-phosphorus product, though the period of observation was short. These and other observations have awakened interest in what may be a disease hitherto undescribed, with a group of clinical phenomena the pathogenesis of which is not yet clear.

I have studied four infants with the same syndrome at the Royal Victoria Infirmary and the Babies Hospital in Newcastle. Three of them had urinary tract infections, which are very frequently but not invariably present in this illness, and were treated with sulphamezathine as well as other drugs in order to attempt to control the extremely resistant infections. The purpose of this paper is threefold: first, to describe the toxic effects of sulphamezathine in three of these children, with special reference to the bone changes in one case; secondly, to correlate these bone changes with changes in the serum calcium-phosphorus products; and thirdly, to emphasize the clinical picture, which may lead a practitioner to suspect the disease so that treatment with sulphamezathine can be avoided.

The biochemical changes in the following three cases are given in Table 1.

Case Histories

Case 1. J.W. was a first child, delivered by forceps after a full-term, normal pregnancy. His birth weight was 7 lb. 6 oz., he had been artificially fed from birth and had accepted solid feeds from 5½ months of age. He had refused cod liver oil and had had no excess of vitamin D. He thrived until the age of 7 months when he began to vomit, became markedly constipated and lost weight.

He was admitted to hospital at the age of 8 months, weighing 16 lb. 4 oz. He was a miserable infant with a greyish colour, who tended to lie still, though he displayed some interest in his surroundings. He was moderately dehydrated and hypotonic, with soft muscles, brisk reflexes and palpable faecal masses in the colon.

Counting pus cells per c.mm. in fresh uncentrifuged specimens of urine (Stansfeld and Webb, 1953) pyuria of up to 420 cells per c.mm. was found and, after two negative cultures, coliform organisms were isolated from the urine on two occasions. Hypercalcaemia and azotaemia were present and the alkali reserve was normal. The packed cell volume and haemoglobin were normal.

The infant became more contented as hydration improved. A course of streptomycin reduced the pyuria only slightly, but after withdrawing the drug it increased and vomiting started again. Sulphamezathine was then given orally and was continued for two weeks, starting with 2 g. daily in four divided doses and reducing the dose to 1 g. daily after six days. At the same time 2 g. sodium citrate was given daily for the first eight days. In two weeks, from a level of 74 mg. per 100 ml. the blood urea had risen to 246 mg. and the serum calcium level had fallen from 15·9 mg. to 12·8 mg. per 100 ml. Neither haematuria not crystalluria was present and the blood urea returned to 73 mg. per 100 ml. in 13 days.

At 11 months of age, on a fluid intake of 1 oz. per lb.

TABLE 1

BIOCHEMICAL INVESTIGATIONS

Date	Serum Protein (g. per 100 ml.)			Serum Calcium (mg. per 100 ml.)	Plasma Phosphorus (mg. per 100 ml.)	Alkali Reserve mEq./l.)	Blood Urea (mg. per 100 ml.)	Serum Chloride (m.Eq. per l.)	Alkaline Phosphatase Units (Jenner and Kay)
	Total	Albumin	Globulin						
Patient J.W.									
14.12.51				15·9		23·8	80		
19.12.51	6·7	5·0	1·7	14·7	6·0				
27.12.51				13·2	5·1	24·5	82	107·2	
10. 1.52				13·1		26·8	40	111·0	
17. 1.52	4·9	3·2	1·7	15·9			74		
18. 1.52						29·5		100·9	
24. 1.52	7·2	5·2	2·0	12·8		22·5	246	102·0	
28. 1.52							147		
31. 1.52	6·3	4·9	1·4	12·7		21·6		98·9	
6. 2.52	7·0	5·5	1·5	12·3		21·2	72		
14. 2.52	6·9	5·0	1·9	13·3		26·8	82	107·0	
3. 3.52	7·0	6·0	1·5	14·3		26·0	74		
11. 3.52	7·5	6·1	1·4	15·6		23·4	47	98·4	
25. 3.52				13·6		20·8	72	103·2	
3. 4.52				12·6		21·0	66	110·8	11·9
29. 4.52	5·4			10·5	6·0	25·6	45	104·9	
13. 5.52	6·3	5·3	1·0	10·3	4·7	24·2	43	102·9	
Sulphamezathine started on 10.1.52.									
Patient O.B.									
26. 3.52	6·3			13·2		22·5	85	116·7	
31. 3.52	5·7			14·1	3·8	19·4	45	100·2	9·3
9. 4.52	6·3			14·4	3·7	20·1	48	108·0	10·8
16. 4.52	5·9			13·4	4·0	19·6	64	110·8	
23. 4.52	6·9			12·4	4·1	17·8	66	112·4	
7. 5.52	6·6	4·8	1·8	14·8	3·4	20·4	55	108·5	
20. 5.52	6·9	4·9	2·0	13·3	3·3	19·3	65	109·6	
27. 5.52	6·3	4·6	1·7	13·1		20·4	57	105·8	
22. 7.52	6·8	5·4	1·4	12·0	4·9	18·9	54	107·7	
18. 8.52	6·0			10·5	2·8	19·1	19	111·2	
9. 9.52	6·2	5·3	0·9	10·5	6·4	25·1		103·9	
30. 9.52	6·0			11·0	4·9	23·0	40		
21.10.52				10·4			30		
4.11.52				10·6	4·7	19·5	29		
2.12.52	6·9			13·2	4·7	21·2	37	99·2	
5.12.52	6·5			9·6		13·9	45		
13. 1.53	7·5			10·6	5·0		38		12·4
10. 3.53	8·3	5·8	2·5	11·4	4·6	20·8	37	106·0	16·7
Sulphamezathine started on 2.4.52.									
Patient R.R.									
12. 4.52	6·0			14·1		32·4	76	90·5	
15. 4.52	7·4			17·4	5·1	32·4	57	94·5	
23. 4.52	5·4			10·2	3·5	24·7	50	102·9	
29. 4.52	5·7			11·8	5·3	25·6	70	107·5	
7. 5.52	6·6			15·2	4·3	25·3	82	95·5	
20. 5.52	6·0	4·6	1·4	17·1	5·7		73	97·2	
23. 5.52	6·5	4·9	1·6	15·0		25·6	76	100·0	
28. 5.52	6·0	4·2	1·8	15·2	2·7	25·6	42	99·2	
4. 6.52	6·9	4·3	2·6	9·9	10·4	22·5		97·2	
5. 6.52	6·9			9·7	13·3				
9. 6.52	5·7	4·2	1·5	12·9	8·7	18·2	171	114·3	
16. 6.52	7·5			14·0		17·8	105		
19. 6.52	6·3	5·2	1·1	13·6	8·2	28·5	154	96·0	
28. 6.52	6·8			13·2	7·8	22·6	93	96·0	6·5
3. 7.52	6·6	5·4	1·2	12·6	5·8	27·8	108	98·0	
10. 7.52	5·7	4·0	1·7	12·8	6·1	23·5	142	103·7	
21. 7.52	5·6	4·3	1·3	12·8	9·0	24·4	136	101·0	10·1
31. 7.52	5·7	4·4	1·3	12·4	6·9	14·9	122	99·2	
5. 8.52	7·2	4·8	2·4	12·8	7·5	19·5	116	100·8	9·0
14. 8.52	7·5			14·2	7·1	27·7	110	100·0	13·1
26. 8.52	6·5			12·8	4·3	22·6	115	109·2	
9. 9.52	6·0	4·6	1·4	13·0	7·4	22·5	54	98·3	
7.10.52	7·4	6·0	1·4	14·3	7·8	17·4	83	102·0	
21.10.52				13·7			91		
4.11.52				13·9		21·2	71		11·8
18.11.52				14·4	4·9	16·1		97·3	11·9
1.12.52	5·9			11·5	4·3		107	95·5	
13. 1.53	9·2	5·3	3·9	13·4	4·5		85		9·1
3. 2.53	9·3	5·0	4·3	11·8	6·1	26·0	83		15·1
3. 3.53				13·6		26·0	76	103·0	
22. 4.53	7·2	5·2	2·0	13·2	5·8	22·7	76	98·6	16·4
Sulphamezathine started on 24.5.52.									

for 12 hours, the specific gravity of eight specimens of urine did not exceed 1,010. By 11½ months the pyuria had diminished to 63 cells per c.mm. and two urinary cultures were sterile. Though it was still necessary to force the baby to take fluids by mouth he began to gain weight well and by 13 months of age the serum calcium and blood urea had fallen to normal levels. Apart from a mild hypochromic anaemia, which responded well to iron therapy, he continued to thrive and at 15 months of age weighed 23 lb. 8 oz. No clinical abnormalities were present and he was still perfectly well when last seen at 1 year 11 months. At this time an early morning specimen of urine had a specific gravity of 1,023.

Case 2. O.B., a fifth child, she had been born normally after a full-term, normal pregnancy, her birth weight being 6 lb. When she was admitted to hospital at the age of 9 months she had never been breast fed and had had no excess of vitamin D. Four weeks before her admission she had been treated at home with a sulphonamide for a respiratory infection with vomiting, which lasted three to four days. Four days before admission she again began to vomit and to refuse solid food, preferring clear fluids. She had become pale and fretful.

On examination, she was a small infant with a pale skin, weighing 9 lb. 11 oz. She had soft muscles but her tendon reflexes were very brisk. Pyuria was present intermittently and coliform organisms were isolated from the second and third catheter specimens of urine. It was found that she had hypercalcaemia, azotaemia and a normal alkali reserve. The alkaline phosphatase level was normal and the plasma phosphorus level slightly lowered.

The anorexia continued, with occasional vomiting, and the baby tended to lie rather still, making no attempt to lift herself up. Treatment with sulphamezathine in a dosage of 1·5 g. per day in four divided doses caused a mild sensitivity rash after 10 days, and a slight rise in the blood urea level was recorded after 14 days. Again, there was no crystalluria or haematuria. When the baby was discharged from hospital at the age of 10 months the pyuria had fallen to 21 cells per c.mm. and she weighed 11 lb. Though pyuria and bacilluria were intermittently present, she began to gain weight slowly, and from 13 months of age the blood urea and serum calcium levels fell steadily to normal, though occasional serum calcium values were still raised. She developed a hypochromic microcytic anaemia which was treated by blood transfusion, and after courses of chloramphenicol and terramycin the urinary tract infection was gradually controlled. When last seen at 18 months of age she weighed 18 lb. 5 oz. but appeared quite normal apart from her smallness.

Case 3. R.R. was a second child, born normally after a full-term, normal pregnancy whose birth weight was 7 lb. 12 oz. He had been breast fed only for the first two weeks of life and was admitted to hospital at the age of 6½ months with a history of anorexia and vomiting since 4 months of age, having thrived until then. He was not constipated and had no polyuria; though he had no polydipsia he preferred water to milk feeds. He had had a normal intake of vitamin D.

On examination he was a pale, wasted baby who had intermittent pyuria ranging up to 300 cells per c.mm., with coliform organisms cultured repeatedly from the urine. The serum calcium and blood urea levels were elevated and he was in a state of alkalosis, although when vomiting ceased temporarily and adequate hydration had been established the alkali reserve fell to normal. The plasma phosphorus was normal.

He continued to have anorexia and vomiting, though with gradually diminishing intensity, until the age of 15 months. A course of streptomycin, started three days after his admission, had no effect, and as he had become clinically worse, sulphamezathine in a dosage of 1 g. per day in four divided doses, with potassium citrate, was started. After a further week, during which time he had become extremely ill, severe azotaemia was noted, with hyperphosphataemia and a temporary fall in the serum calcium to normal levels; the biochemical changes are recorded in Fig. 1. No haematuria or

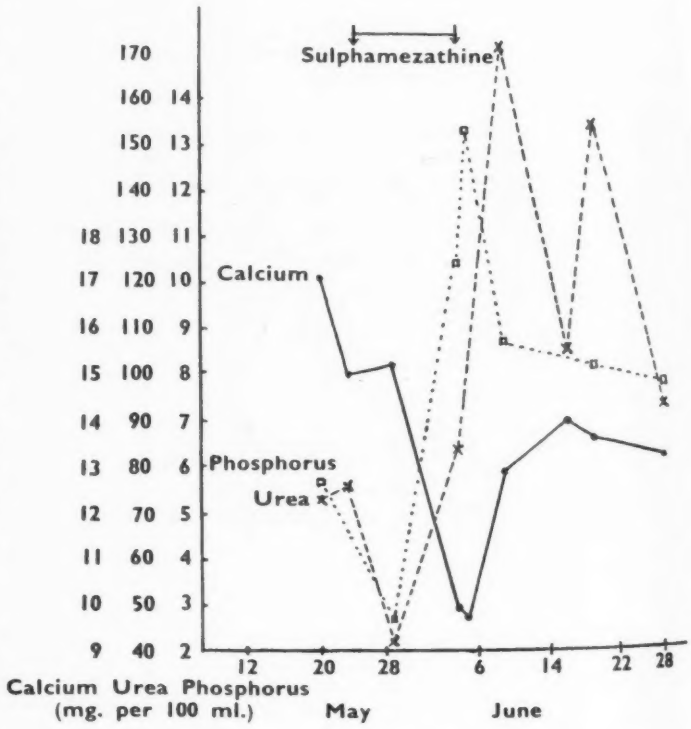

FIG. 1.—Blood biochemical changes in patient R.R. following sulphamezathine therapy.

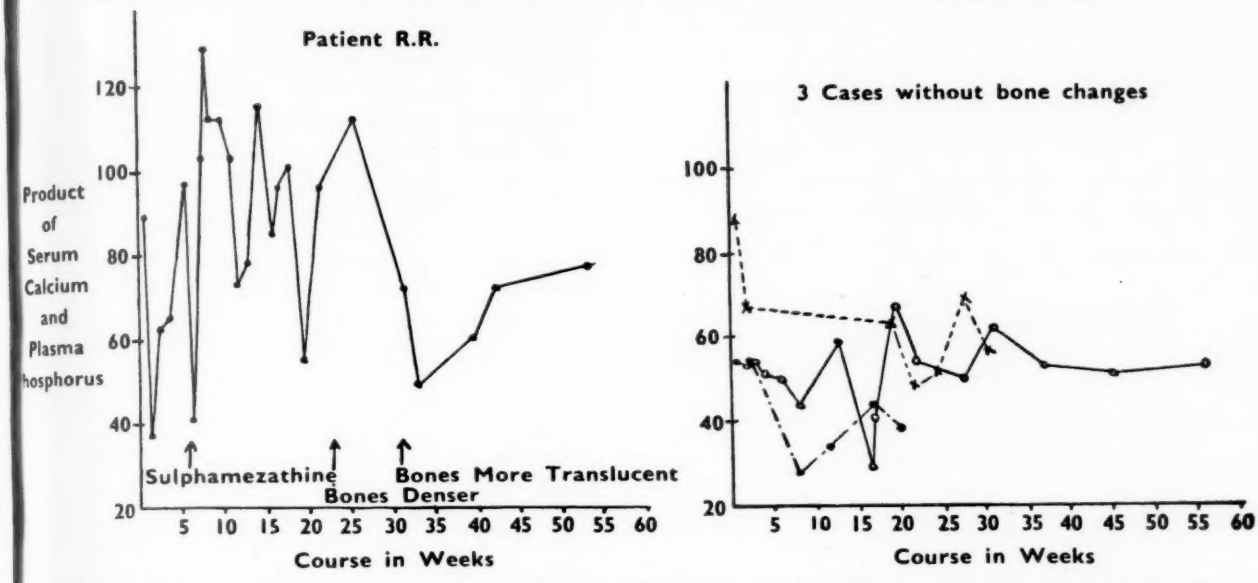

FIG. 2.—Calcium-phosphorus products in patient R.R. compared with three cases of idiopathic hypercalcaemia without comparable bone changes.

crystalluria was observed, though frequent microscopical examinations of urine were made. Following this, though the serum calcium returned to its former high levels within a few days, the blood urea level remained elevated and the plasma phosphorus level was raised for four months. As bacilluria and pyuria persisted, chloramphenicol was given, with little improvement and then a course of terramycin, after which pyuria and bacilluria gradually disappeared.

He developed a normochromic, normocytic anaemia, the haemoglobin being 9·2 g. per 100 ml. At 11 months of age he weighed only 13 lb. 3 oz. and at this age, on a fluid intake of 1½ oz. per lb. over 24 hours, the specific gravities of 11 specimens of urine were not higher than 1,010. At the time of writing he is 21 months old, weighs 17 lb. 4 oz. and still has hypercalcaemia and azotaemia. Though he appears to be mentally normal he has only recently begun to sit unaided.

The radiological changes in the bones are described below. Radiographs of bones of five other cases of idiopathic hypercalcaemia in infants studied in Newcastle showed no abnormality other than growth lines in four.

The bone changes were bilateral and symmetrical and the first changes were seen at 1 year, by which time he had had a markedly elevated serum calcium-phosphorus product for four months. The distal end of the ulna was cupped and of the radius irregular in outline, with single, dense transverse lines at the ends of these bones. The vertebrae looked denser than normal but radiographs of the skull were not taken at this stage.

At 13 months of age radiographs of the hands, taken for the first time, in the same film as a normal control, showed single, dense transverse bands at the distal ends of the metacarpals and at the proximal ends of the proximal phalanges.

At 14 months of age radiographs were taken of the legs. These showed obvious growth lines at the upper ends of the tibia and fibula and the upper and lower ends were cupped. The lower femoral epiphysis had a thin surrounding halo of more translucent bone, sharply demarcated from the central nucleus of bone which was densely calcified (Fig. 3). Radiographs of the skull

FIG. 3.—Radiograph of legs in patient R.R. showing dense epyphysea l centres and translucent surrounding bone. Bone at ends of metaphyses is more translucent. Some failure of tubulation is present in the distal third of the femur.

showed considerable increase in density at the base compared with a normal control (Fig. 4).

At 18 months of age radiographs of the legs showed more growth lines and the halo of translucent bone was wider in the lower femoral epiphysis, and had appeared in the upper tibial epiphysis. Adjacent to the dense transverse bands at the ends of these bones were areas

of more translucent bone, corresponding with the epiphyseal halos, showing that recently formed bone was less densely calcified. Similar epiphyseal halos and areas of more translucent bone at the ends of the metaphyses were present at the lower end of the humerus and the upper end of the radius. Radiographs of the vertebrae now showed that the bodies were so dense that the paired nutrient foramina in each body showed up in contrast. The increased density at the base of the skull was now even more obvious.

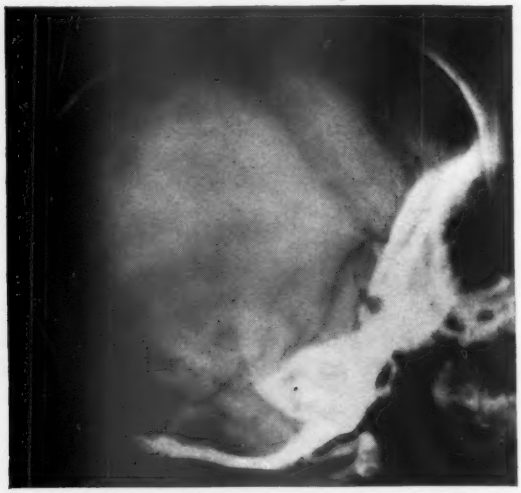

FIG. 4.—Radiograph of skull in patient R.R. showing marked thickening at the base.

Comment

In this department it has become the custom to give long courses of sulphamezathine for urinary tract infections in infancy, on account of the liability of the infection to recur with permanent effects on the kidneys. This had previously been found to be a safe procedure.

Sulphamezathine had been administered to another infant with idiopathic hypercalcaemia with no ill effect, and some of the cases described by Lightwood (1952) had received sulphonamides, but over shorter periods, without complications. Following the complications in my cases, the fact that toxic effects following sulphonamide therapy had not been noted previously led me to consider the possible effect on the kidneys of the sodium citrate given to patient J.W. and the potassium citrate given to patient R.R. In the case of J.W., on the day before alkali therapy was discontinued, a blood urea value was lower than it had been, but had risen to 246 mg. per 100 ml. seven days later. The alkali reserve, over this seven-day period, had fallen from 29·5 mEq. per litre to 22·5 mEq. per litre. Thus, though the alkali reserve had risen to abnormal levels it was not accompanied by increased azotaemia at that time. The evidence suggests that the alkali therapy did not play an important role in the causation of the increased renal damage. In the case of R.R. there was no alkalosis while the potassium citrate was being given so that the drug played no obvious part in the increased renal dysfunction in this case either.

It is difficult to advance evidence as to how sulphamezathine caused such severe renal dysfunction. It is unfortunate that blood levels were not estimated as it seems likely that renal excretion of the drug was impaired and one would therefore have expected high blood levels. In each case the toxic effects were only observed after a long course of the drug, on the tenth day in O.B., after 11 days in R.R. and after 14 days in J.W., though in the latter cases biochemical changes had certainly begun earlier. In an effort to explain the bone changes in patient R.R., the products of serum calcium and plasma phosphorus in his case were compared with those of three other cases of the same syndrome in which similar bone changes did not occur (Fig. 2). This comparison showed the product to be very much higher over a long period of time in the case with the striking bone changes.

The sequence of events in patient R.R. seems to be as follows. Sulphamezathine aggravated existing renal dysfunction with resulting hyperphosphataemia. After an initial fall, the serum calcium returned to its former high levels and the calcium-phosphorus product remained persistently and markedly raised for a period of four months, at the end of which time sclerotic changes were first definitely noted though some earlier radiographs had been suspicious. After a further two months, and after a gradual fall in the calcium-phosphorus product, the density of recently formed bone diminished. It is therefore suggested that the osteosclerosis in this case may be the direct result of increased calcification due to a high product of serum calcium and plasma phosphorus.

It would seem unwise to treat with sulphamezathine any infant of the age of about 3 to 8 months in whom the symptoms suggest this illness, unless biochemical investigations have excluded it. If a short course of treatment is given the infection is liable to recur, and if a long course is given, severe toxic effects may result. It is important, therefore, that a practitioner should be familiar with the clinical picture.

Clinical Picture

In most cases this illness starts suddenly in a healthy infant of either sex, of 3 to 8 months of age. Occasionally, however, the first symptoms may

follow another illness such as an intussusception or an upper respiratory infection. The first symptoms are anorexia and vomiting. The anorexia is characteristically worse for solid feeds, which are resolutely refused, and water or other clear fluids are preferred to milk. Often milk feeding has to be carried out by means of a spoon and even then several efforts are sometimes required to induce the infant to swallow a single mouthful. This type of anorexia may provide an important clue to the diagnosis though it is also present in renal acidosis, with which this disease is sometimes combined. Thirst and apparent polyuria may be noted by the mother but they are not presenting features of the illness. Constipation is a common finding and may be severe, with the passage of hard, pebble-like stools for several months. The infant is usually contented but may have periods of irritability when the vomiting is severe.

As the disease progresses the complexion becomes pale or greyish, the child loses weight, and the mother may note that the infant has become pale and floppy and the limbs soft. She may state further that though he appears to be normal mentally he has not begun to sit up at the normal age. In cases in which the urinary tract infection has been treated, usually after two to five months, but sometimes after a longer period, a steady weight begins, the body tone improves and the child begins to sit up. In most cases recovery is eventually complete and full health restored by the age of 18 months. A fatal outcome is most unusual but one out of seven patients studied at Newcastle died rather suddenly. A necropsy was not obtained.

On clinical examination in the acute stage of the disease one is confronted by a wasted, limp infant who nevertheless displays interest in his surroundings. In contrast with the thin extremities the abdomen may appear full and this may be accounted for by constipation and muscular hypotonia. There are often palpable faecal masses in the colon. Signs of dehydration, though usually present, are not sufficiently marked to warrant intravenous therapy; in fact the wasting is a more striking feature. The musculature is soft and the tone reduced but the tendon reflexes are brisk. Dentition is normal. A hypochromic microcytic anaemia may be present but this generally occurs late in the course of the disease. Mild intermittent pyrexia is often found. Pyuria is extremely common but is not invariably found and when it is coliform organisms are usually intermittently cultured. If proteinuria is noted it is generally slight. The hypercalcaemia is independent of the level of plasma phosphorus, which is normal or slightly lowered. The calcium and phosphorus changes in patient R.R. provide the first instance of a reciprocal relationship in my experience of the disease, the fall in serum calcium being apparently secondary to the rise in phosphorus. Since one of the theories of the syndrome is that calcium excretion is diminished as a result of renal dysfunction, with resultant hypercalcaemia, this fall in serum calcium with a known exacerbation of renal damage is not in accord with the theory, unless in this particular case other mechanisms which lower the level of the serum calcium were also operating.

Summary

Of three cases of idiopathic hypercalcaemia of infancy, receiving sulphamezathine therapy for urinary tract infections, two developed a severe and one a mild degree of azotaemia. In one child, moderate azotaemia was still present 13 months later.

In the same child, as a result of renal dysfunction, a rise in plasma phosphorus occurred, causing a markedly elevated product of serum calcium and plasma phosphorus, which persisted for four months. Sclerotic changes developed in the bones of this patient and it is suggested that the high calcium-phosphorus product was responsible for this.

The clinical features of the illness are described, with a warning against the use of sulphamezathine for the commonly associated urinary tract infection.

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THE EFFECT OF CHLORAMPHENICOL IN SALMONELLA ENTERITIS OF INFANCY

BY

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During the year 1951, in the Royal Children's Hospital, Melbourne, chloramphenicol was used for the treatment of numerous children with infective diarrhoea, and an impression was gained that it was relatively ineffective in the treatment of Salmonella enteritis, despite the high sensitivity of the group to chloramphenicol *in vitro*. Experimental work on mice by Seligmann and Wassermann (1949) indicated that chloramphenicol was bacteriostatic rather than bacteriocidal to Salmonella. The clinical results of Ross, Burke, Rice, Washington and Stevens (1950), Weiner and Liebler (1951) and Kunstadter, Milzer and Kagan (1951) on small series of patients supported this finding, but the variable clinical course of Salmonella enteritis, even when untreated, made assessment of the efficacy of antibiotics difficult. In some cases the organism temporarily disappeared from stools during treatment, but reappeared soon after cessation of therapy. Fison and Singer (1950), in treating an outbreak of infantile diarrhoea due to Salmonella, formed the opinion that chloramphenicol was responsible for decreasing morbidity and mortality, and other reports of single cases or small series supported this view.

At the Royal Children's Hospital, Melbourne, from November, 1951, to March, 1953, a controlled clinical therapeutic trial to determine the efficacy of chloramphenicol on infants suffering from Salmonella enteritis was carried out. During this period, 390 infants less than 2 years of age were admitted to hospital with the diagnosis of infective diarrhoea. Salmonella were grown from the stools of 98 of these infants, 51 of whom were studied in the controlled trial.

Methods

As soon as an infant with diarrhoea had been admitted to hospital, two rectal swabs following the passage of stools were cultured immediately on 'difco' S.S. agar and in tetrathionate broth. From these two primary cultures subsequent isolation and identification were performed. If a culture of either specimen grew Salmonella, it was considered that the infant fulfilled the bacteriological requirements for admission to the controlled therapeutic trial.

In addition, all infants included in the trial were less than 2 years of age, were in good health before the onset of enteritis, and were free from parenteral infection. In each case, the enteritis was of less than one week's duration, and no specific treatment had been given before admission to hospital. A history of feeding derangement precluded admission to the series. Although this pre-selection reduced the number of infants studied to approximately half the cases of Salmonella enteritis admitted to hospital the validity of the results was improved by the elimination of variables. All infants were moderately ill with eight to 20 bowel actions per day. Clinical dehydration severe enough to warrant intravenous infusion was the exception, and as preliminary observations had revealed no obvious relationship between initial dehydration and the duration of the illness, this physical feature played no part in pre-selection.

Treated and control infants were selected on the basis of 'odds and evens' taken from a table of random numbers. After it had been decided by the medical observer that an infant fulfilled the clinical and bacteriological requirements the ward sister allotted it to the treated or untreated group, but the category was not known to the medical observer. Thus, as there was no alternation of cases, observations were quite unbiased.

Treated infants received oral chloramphenicol, 120 mg./kg. of body weight per day, at six- to eight-hourly intervals for 10 days. Apart from chloramphenicol, treated and control infants received the same treatment. A similar feeding routine was established in each case, modified only by the course of the illness and the age of the infant. After an initial starvation of 24 hours, during which time water with 5% glucose and a solution of sodium and potassium salts were given, the feeding was changed

TABLE 1

AGE GROUPING OF 25 INFANTS TREATED WITH CHLORAMPHENICOL AND 26 CONTROLS

Category	Less than 3 months	3–6 months	6–12 months	12–18 months	18–24 months
Treated ..	4	5	13	3	Nil
Controls ..	4	8	9	3	2

to half-strength skimmed milk, thence to full-strength skimmed milk, and finally, to whole dried milk, occasionally through an intermediate stage of half-cream dried milk, with formula according to age. Symptomatic treatment was confined to sedation, and topical applications to rashes and excoriations. Although Salmonella enteritis had a higher incidence during the summer months, infants suffering from this disease were admitted to hospital throughout the winter. To avert complicating respiratory infections, penicillin was sometimes given to untreated infants, and although this introduced another variable, it was considered to be less confusing than a complicating respiratory infection of which only the mildest were encountered. Ordering penicillin for untreated cases with respiratory infections was the responsibility of the ward registrar.

For 10 days following isolation of Salmonella stools were cultured on every second day from both treated and control infants, and, after the conclusion of treatment, on every third day until discharge from hospital. The infants were reviewed one week later in the out-patient department when a rectal swab was cultured.

Results

Of a total of 98 infants with Salmonella infection, 51 were included in the experiment. Of these 51 infants, 48 were infected by *S. typhi-murium*, two by *S. adelaide*, and one by *S. derby*. Twenty-five of the 51 infants were treated, and 26 acted as controls, a distribution as good as if treatment had been allotted to alternate cases. The 25 treated infants consisted of 15 males and 10 females, and 14 males and 12 females comprised the untreated group of 26 infants. The infecting organisms in the treated group were *S. typhi-murium* (23 cases), *S. adelaide* (one case) and *S. derby* (one case), and in the untreated group, *S. typhi-murium* (25 cases) and *S. adelaide* (one case). Age grouping was reasonably well distributed (Table 1). The mean age of the treated infants was 7·44 months, the range being from 1 to 17 months, while the mean age of the untreated group was 8·07 months, with a range of 2 to 21 months. The effect of chloramphenicol was assessed both clinically and bacteriologically.

Clinical Assessment

It was considered that a clinical cure had been obtained when an infant was tolerating a full-strength feed, and was excreting stools of normal consistency and number for that particular age group. This decision was arbitrary and was dependent on the clinical experience of the medical observer. By the time this stage had been reached the infant was invariably afebrile and free from other abnormal features. Weight gain had usually begun but was not considered essential as an index of clinical cure, as a small infant after a protracted illness sometimes would take several weeks before he had gained satisfactorily. On this basis, clinical results of chloramphenicol are shown in Tables 2a and 2b. The mean duration in days from the beginning of the illness to clinical cure was 19·52

TABLE 2a

MEAN DURATION AND RANGE IN DAYS FROM START OF ILLNESS TO CLINICAL CURE

Category	Less than 3 months	3–6 months	6–12 months	12–18 months	18–24 months
Treated ..	25·75 (8–46)	18·4 (12–24)	19·3 (10–35)	14·0 (12–16)	Nil
Controls ..	24·25 (19–25)	21·1 (12–38)	20·4 (10–38)	12·6 (3–18)	13·5 (10–17)

TABLE 2b

MEAN DURATION AND RANGE IN DAYS FROM START OF TREATMENT TO CLINICAL CURE

Category	Less than 3 months	3–6 months	6–12 months	12–18 months	18–24 months
Treated ..	21·75 (6–41)	12·2 (9–16)	14·8 (7–32)	10·3 (7–12)	Nil
Controls ..	18·5 (11–30)	15·9 (9–33)	13·75 (3–30)	7·3 (0–15)	8·5 (8–9)

days, ranging from eight to 46 days (standard deviation 9·24 days) for treated infants and 18·96 days ranging from three to 38 days (standard deviation 9·10 days) for control infants. The mean duration in days from the beginning of treatment to clinical cure was 14·90 days, ranging from six to 41 days (standard deviation 9·09 days) for treated infants, and 13·46 days, ranging from nil to 33 days (standard deviation 8·27 days) for control infants.

In Tables 2a and 2b the mean duration and range in days have been tabulated according to age. There appears to be an inverse relationship of age to length of illness, but the number of cases in each age category is too small and the range too large to be significant. Three infants only required intravenous infusion; two were in the control group and one was treated. The two untreated infants were clinically cured in 10 and 36 days from the beginning of their illnesses, and in seven and 33 days from when treatment would have begun. The treated infant was clinically cured in 19 days from the beginning of his illness and in 18 days from the start of treatment. The treated infant infected with *S. adelaide* was clinically cured in 18 days after the start of illness, and in 16 days following the beginning of treatment. The treated infant infected with *S. derby* was clinically cured in 17 days after the beginning of his illness, and in 13 days after the start of treatment. The control infant infected with *S. adelaide* was cured in 11 days after his illness started and in nine days from when treatment would have been begun. It appears that the clinical course of infection with these two strains of Salmonella is similar to that with *S. typhi-murium*, as far as one can determine from three cases.

Bacteriological Assessment

The Salmonella group was moderately sensitive to chloramphenicol *in vitro*, and most organisms tested were sensitive to a concentration of 5 μg./ml. A few were resistant to 5 μg./ml. but were sensitive to 10 μg./ml. The effect *in vivo* was completely unpredictable both in treated and untreated infants. Isolation of Salmonella was obtained at various stages of the clinical course, with comparable frequency in both treated and untreated cases. The results have been categorized arbitrarily in Table 3. At the time of discharge from hospital, Salmonella could still be cultured from the stools of 10 treated infants and 11 untreated infants. In four treated infants and in three controls, the organism had temporarily disappeared during the stay in hospital, but was present on discharge. Forty-three of the 51 infants, comprising 22 treated and 21 control cases, were examined in the out-patient department one to two weeks after discharge from hospital, and rectal swabbings were cultured from each. Salmonella was isolated from eight treated and eight control infants. The behaviour of Salmonella was unpredictable in the control infants as well as in those treated with chloramphenicol, and on these figures even a temporary bacteriostatic effect of the drug *in vivo* could not be claimed, as in 15 untreated, as well as in 15 treated cases, the organism could not be demonstrated on stool culture at the time of discharge from hospital.

Discussion

Although minor epidemics may occur during summer, *S. typhi-murium* appears to be endemic in Melbourne, and infants suffering from Salmonella enteritis are admitted to hospital each week. However, during a period of 17 months with the pre-selection used in the present procedure, only 51 infants less than 2 years of age were found to be suitable for a controlled therapeutic trial of chloramphenicol. Restriction to a narrower group was thus not justified, despite a tendency for the clinical course of the disease to be protracted in the early months of life. The wide range in duration of the natural course of the disease diminishes the significance of results, but, as it was impossible to predict the duration or severity of the illness at its start, a further pre-selection to demonstrate the efficacy of chloramphenicol better was impracticable. Despite these incompletely controlled variables, results at least demonstrate that in the practical management of Salmonella enteritis in infants administration of

TABLE 3

TIME OF DISAPPEARANCE OF SALMONELLA FROM STOOL CULTURES RELATIVE TO TREATMENT OR WHEN TREATMENT WOULD HAVE BEEN GIVEN TO CONTROLS

Category	Isolated on 1st pre-treatment Stool Culture but not Subsequently	Disappearance during Treatment without Reappearance	Disappearance during Treatment with Recurrence during or after Treatment	Disappearance after Treatment before Discharge from Hospital	Present throughout Stay in Hospital and on Discharge
Treated ..	2	9	8	Nil	6
Controls ..	1	7	7	3	8

chloramphenicol in adequate dosage has no effect in altering the clinical course of the disease, or of significantly affecting the growth of the organism in the stools. There was no evidence that the drug adversely affected the course of the disease, but continuation of its use would appear unnecessary and uneconomical. Serum concentrations of chloramphenicol were not estimated in this trial. The sensitivity of the Salmonella group *in vitro* was of the same order as that demonstrated by McLean, Schwab, Hillegas and Schlingman (1949) and by other workers since then.

Summary

Fifty-one infants less than 2 years old suffering from Salmonella enteritis were subjected to a controlled therapeutic trial to test the efficacy of chloramphenicol in this disease.

Forty-eight of the infants were infected by *S. typhi-murium*.

Chloramphenicol at a dose of 120 mg./kg./day had no effect in influencing the rate of clinical recovery.

Despite a high degree of sensitivity to chloramphenicol *in vitro*, the growth of Salmonella in the bowel was not significantly affected by the drug.

Doctors D. H. McCredie, M. Clare McKinnon, J. J. M. O'Neill, and M. J. Robinson, of the resident medical staff, Royal Children's Hospital, assisted in the practical management and observations of the infants.

Sisters J. R. Scott, M. M. McQuarrie, and M. Houston were responsible for the nursing care and observations, and the allotment of infants to the treated or control groups.

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THE FAT AND WATER CONTENT OF THE LEFT AND RIGHT LIVER BEFORE AND AFTER BIRTH

BY

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Asymmetrical foamy-celled change in the right lobe of the liver in newborn infants was noted by Gruenwald (1949), and we have described (Emery, 1952) a rapid degeneration of the left physiological lobe of the liver following birth. These asymmetrical changes in the liver are associated with the different blood supply to the right and left physiological lobes *in utero* and are probably of great importance in metabolic changes in the newborn and in the study of later intra-uterine diseases. It is also obvious that the liver in the foetus and in the newborn should not be studied as a single organ but as two distinct but united organs, that is, a right and left liver.

In order to investigate this problem further we have examined the fat and water content, both histologically and chemically, of the livers of children dying prematurely, at full term during the neonatal period and in some older children. Great differences between the contents of the right and left lobes were found in many cases, but before such findings could be assessed it was necessary to study the normal variation.

Very little information is to be found in the literature on the amount of fat occurring normally in the human embryo in the neonatal period or concerning the lobe differences. Also examinations that have been reported have apparently not considered the pathological fatty changes now known to occur in the liver *in utero* and thus did not distinguish between normal and abnormal livers (Widdowson and Spray, 1951).

Dorkin and Weinberg (1949) studied the histologically demonstrable fat in the livers of stillborn and newborn infants. They endeavoured to correlate fat content with maturity and concluded that the storage of fat reaches its maximum during the last month of gestation. Needham (1931) had also found an increase of fat in the human embryo as a whole from five to nine months but did not indicate if liver fat as such increased over this period.

Rourke and Stewart (1942) examined the liver with regard to its uniformity with respect to the concentration of fat, water and vitamin A in different parts of the same liver and concluded that on the whole fats and water are uniformly distributed. Billing, Conlon, Hein and Schiff (1953) estimated the liver lipids in man in different parts of the liver by means of specimens taken by needle biopsy. They also found relative uniformity throughout the liver and that the histology and chemical estimation of fat content paralleled each other. Most of these investigations, however, were done on livers from adults.

This communication records an attempt to establish the normal fat and water contents of the left and right livers in later foetal and early neonatal life.

Materials and Methods

For about a year the fat and water content of the left and right liver has been estimated on all (134) stillborn and neonatal infants coming to necropsy. The livers were divided into three parts by two cuts, one along the line of the anterior ligament and ductus venosus, that is, cutting off the anatomical left lobe. The second cut was taken from the tip of the gall bladder to the inferior vena cava through the base of the gall bladder to the hilum. This cut divides the liver into the physiological left and right lobes. The central part of the liver constituting the median part of the left physiological lobe was discarded after weighing. Blocks of distinctive shape were taken for histology from the left and right lobes, the remainder of which were then separately cut into thin slices by a very sharp knife and blotted to remove as much blood as possible.

For chemical analysis the whole of the sliced lobes were weighed and dried on a hot plate at 95°-100° C. until a constant weight was obtained. From these values the water content was calculated. After grinding the tissue to a powder, duplicate samples were weighed,

boiled for 30 minutes in 30% hydrochloric acid, the fat extracted with ether, the ether evaporated, and the residual fat weighed after cooling in a vacuum desiccator. The fat content was then expressed as a percentage of the dry weight.

Sections from both lobes were carefully examined and livers showing any cellular abnormality in either lobe were excluded. Frozen sections were stained for fat in many instances and any liver showing fatty droplets was excluded. However, no liver was seen in paraffin sections to contain fat that did not show other changes microscopically which would in any case have caused its exclusion from the normal series. Cases showing known intra-uterine disease, such as Rh incompatibility and diseases of the placenta, were also excluded even when no abnormality was seen in the liver. This necessitated excluding about two-thirds of the cases examined.

The maturity of the infants was estimated on a combination of the duration of pregnancy and the crown-rump, crown-heel length of the infants using the range given by Streeter (1920) and Scammon and Calkins (1923).

Results

In order to assess any significant difference between the right and left lobes it was necessary to analyse the differences between duplicates of each lobe.

It was found that the range of difference from duplicate fat estimations on 96 specimens was 0-1·6 g. per 100 g. dry liver, with a mean difference of 0·43 g. (standard deviation 0·47). From these figures any difference greater than 1·88 g. % was regarded as significant.

Similarly the duplicate analyses of water content were statistically analysed with the following results. There was a range of difference from 0 to 1·7% with a mean difference of 0·3 (standard deviation 0·3). Therefore any figures varying by more than 1·2 % may be regarded as significantly different.

Water Content of Liver before Birth. No significant difference was found in the water content of the livers from foetuses of six, seven, eight and nine months' gestation or in water content of the left and right lobes at any age (Table 1). In livers of 10 or more months' gestation there appeared to be a small diminution in water content affecting the liver symmetrically.

The variation in water content within an age group was wider than that between different age groups. All livers showing a water content of 80% or more were from 'immature' infants. The difference in water content of different livers in the same age group was much greater than any difference between the different lobes of the same liver.

Water Content of Livers after Birth. Since infants of different maturity appeared to have differing liver water contents it would seem ideally desirable to study post-natal changes in different maturity groups. The data, however, for this were much too small, hence the whole series of live births is considered together in Table 2 and Fig. 1.

A survey of the figures showed no significant changes in water content with age, as wider variations occurred in each group than between different age groups. On the other hand, water contents of 79% and over were only found in infants under the age of 12 hours. But these levels are themselves explicable on the immaturity of some of the individuals constituting this group. There would seem to be no gross diminution in water content after birth.

TABLE 1

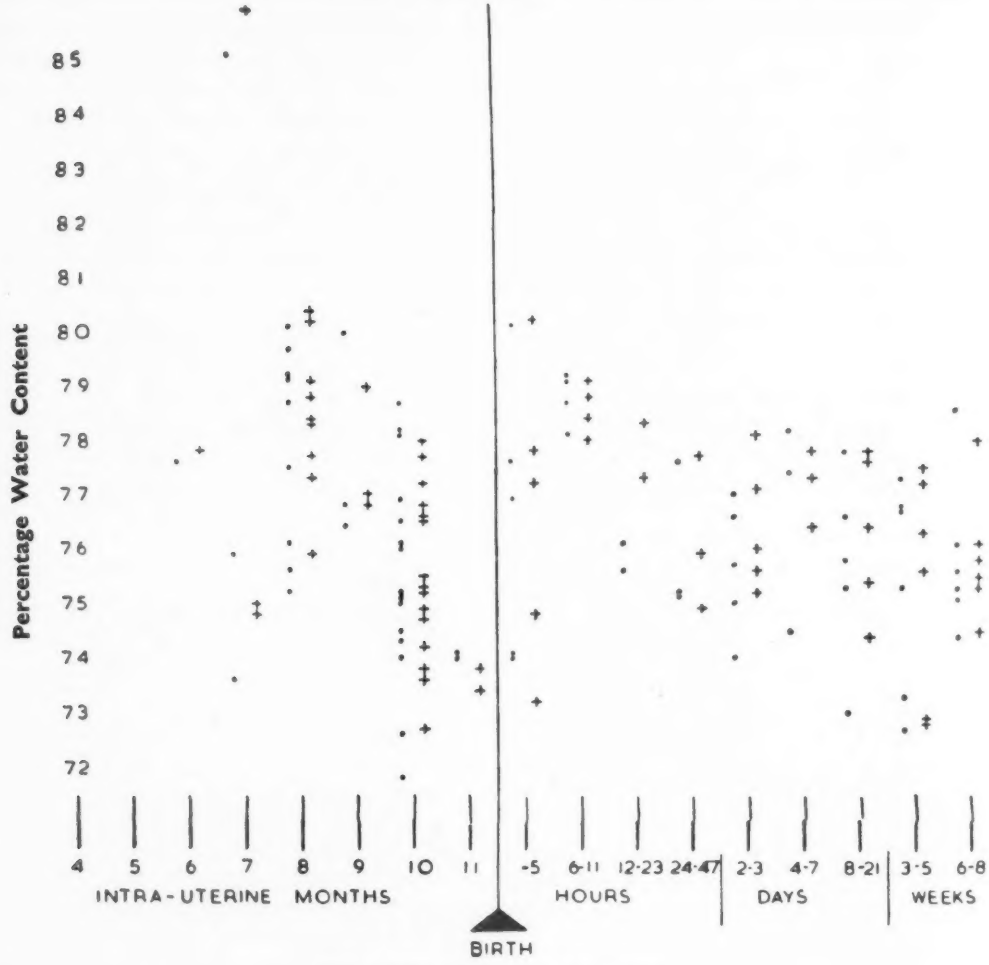
WATER CONTENT OF RIGHT AND LEFT LOBES OF THE LIVER OF INFANTS DYING BEFORE THE AGE OF 24 HOURS RELATED TO MATURITY

Maturity (months)	Percentage Water Content of Left and Right Lobes									Range	Average
6	R. 77·6									—	77·6
	L. 77·8										77·8
7	R. 75·9	85·1	73·6							73·6–85·1	78·2
	L. 75·0	86·0	74·8							74·8–86·0	78·6
8	R. 78·7	75·6	76·1	75·2	79·1	79·2	79·7	80·1	77·5	75·2–80·1	77·9
	L. 78·4	78·3	77·3	75·9	79·1	78·8	80·4	80·2	77·7	75·9–80·4	78·5
9	R. 76·8	80·0	76·4							76·4–80·0	77·7
	L. 76·8	79·0	77·0							76·8–79·0	77·6
10	R. 76·5	74·0	74·5	71·8	75·0	76·0	76·1	75·2	78·2		
	L. 74·7	75·3	75·5	72·7	73·8	76·6	76·5	74·2	76·8	71·8–78·7	
										72·2–78·0	75·5
	R. 72·6	78·7	74·3	76·9	75·2	78·1					75·5
	L. 73·6	77·7	75·3	77·2	74·9	78·0					
11	R. 74·0	74·0								74·0	74·0
	L. 73·8	73·5								73·5–73·8	73·7

TABLE 2

WATER CONTENT OF LIVER RELATED TO THE IMMEDIATE POST-NATAL AGE OF THE CHILD AT DEATH

Age		Percentage Water Content						Range	Average
Birth–5 hours ..	R.	74·0	74·0	76·9	80·1	77·6		74·0–80·1	76·5
	L.	73·2	73·8	77·2	80·2	77·8		73·2–80·2	76·4
6–11 hours ..	R.	78·1	78·7	79·1	79·2			78·1–79·2	78·9
	L.	78·0	78·4	79·1	78·8			78·0–79·1	78·6
12–23 hours ..	R.	76·1	75·6					75·6–76·1	75·8
	L.	77·3	78·3					77·3–78·3	77·8
24–47 hours ..	R.	77·6	75·2	75·2				75·2–77·6	76·0
	L.	77·7	74·9	75·9				75·9–77·7	76·2
48 hours to 3 days	R.	74·0	75·7	76·6	75·0	77·0		74·0–77·0	75·7
	L.	75·2	76·0	77·1	75·6	78·1		75·2–78·1	76·4
4–7 days ..	R.	74·5	78·2	77·4				74·5–78·2	76·7
	L.	76·4	77·8	77·3				76·4–77·8	77·8
8–21 days ..	R.	76·6	73·0	77·8	75·3			73·0–77·8	75·7
	L.	77·6	74·4	77·8	76·4	75·4		74·4–77·8	76·3
21 days–5 weeks ..	R.	77·3	76·7	75·3	72·7	73·3	76·8	72·7–77·3	76·4
	L.	77·5	77·2	75·6	72·8	72·9	76·3	72·8–77·5	76·5
6–8 weeks ..	R.	78·6	75·6	76·1	75·3	75·1	74·4	74·4–78·6	75·8
	L.	78·0	75·3	75·8	76·1	75·5	74·5	74·5–78·0	75·8



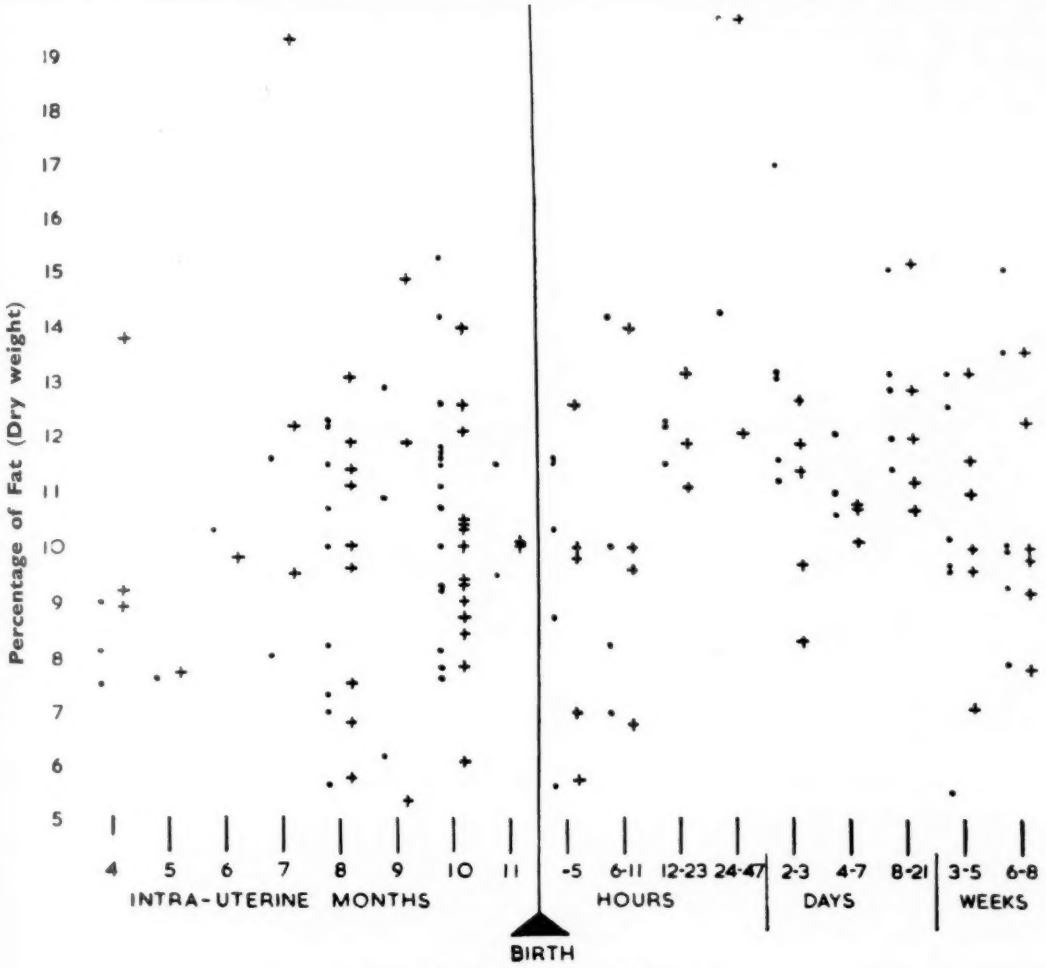
Spot = Right Liver. + = Left Liver.

FIG. 1.—Chart showing the distribution of percentage water content of 21 stillborns and 39 children dying after birth related to maturity and post-natal age.

TABLE 3

FAT CONTENT BASED ON DRY WEIGHT OF THE RIGHT AND LEFT LIVERS OF INFANTS DYING BEFORE THE AGE OF 24 HOURS RELATED TO MATURITY

Maturity (months)	Percentage Fat of Dried Weight									Range	Average
4	R.	8·1	7·5	9·0						7·5–9·0	8·2
	L.	8·9	13·8	9·2						8·9–13·8	10·6
5	R.	7·7								—	7·7
	L.	7·6									7·6
6	R.	10·3								—	10·3
	L.	9·8									9·8
7	R.	11·6	18·4	8·0						8·0–18·4	12·7
	L.	12·6	19·3	9·5						9·5–19·3	10·3
8	R.	7·0	10·7	5·7	7·3	8·2	10·0	11·5	12·2	7·0–12·2	9·4
	L.	9·6	11·4	5·8	7·5	6·8	10·0	11·1	11·9	5·8–11·9	9·7
9	R.	6·2	12·9	10·9					13·1	6·2–12·9	10·0
	L.	5·4	14·9	11·7						5·4–14·9	10·3
10	R.	14·2	15·3	11·5	8·1	11·1	11·7	10·0	7·8	7·6–15·3	10·8
	L.	14·0	12·1	12·6	8·7	8·4	10·5	9·0	7·8	6·1–14·0	9·9
	R.	12·6	11·7	9·3	9·2	7·6	11·6			9·5–11·5	
	L.	10·3	10·0	9·4	10·0	6·1	9·3				
11	R.	9·5	11·5							—	10·5
	L.	10·0	10·0								10·0



Spot = Right Liver. + = Left Liver.

FIG. 2.—Spot graph showing the distribution of percentage (dried weight) at content of 25 stillborn and 39 children dying after birth, related to intra-uterine maturity and post-natal age.

TABLE 4

FAT CONTENT BASED ON DRY WEIGHT OF THE RIGHT AND LEFT LOBES IN HISTOLOGICALLY NORMAL LIVERS OF CHILDREN DYING AT DIFFERENT AGES AFTER BIRTH

Age		Percentage Fat Content						Range	Average
Birth to 5 hours ..	R.	5·7	11·5	11·5	7·7	10·3		5·7–11·5	9·3
	L.	5·8	12·6	10·0	7·0	9·8		5·8–12·6	9·0
6 –11 hours ..	R.	14·2	7·0	10·0	8·2			7·0–14·2	9·9
	L.	14·0	9·6	10·0	6·8			6·8–14·0	10·1
12–23 hours ..	R.	12·3	12·2	11·5				11·5–12·3	12·0
	L.	13·1	11·9	11·1				11·1–13·1	12·0
24–47 hours ..	R.	15·3	19·7					15·3–19·7	17·5
	L.	12·1	19·7					12·1–19·7	15·9
48 hours to 3 days	R.	17·0	13·2	13·1	11·6	11·2		11·2–17·0	13·2
	L.	11·9	8·3	12·7	9·7	11·4		8·3–12·7	10·8
4–7 days ..	R.	10·6	11·0	12·1				10·6–12·1	11·2
	L.	10·1	10·7	10·8				10·1–10·8	10·5
8–20 days ..	R.	12·0	15·1	12·9	11·4	13·2		11·4–15·1	16·1
	L.	11·2	15·2	12·9	10·7	12·0		10·7–15·2	15·5
31 days to 5 weeks	R.	9·7	5·7	13·2	10·2	12·6	9·6	5·7–13·2	10·2
	L.	10·0	7·1	13·2	11·0	11·6	9·6	7·1–13·2	10·4
6–8 weeks ..	R.	14·1	10·0	13·6	9·3	10·0	7·9	9·3–14·1	10·8
	L.	12·6	10·0	12·3	9·2	9·8	7·8	9·2–12·6	10·3

Fat Content in Livers *in Utero*. The fat content of these apparently normal livers showed a greater variation than the water content. The complete range found was from 5·4 to 19·3%. Study of the figures (Table 3) and of the distribution of levels (Fig. 2) suggested that variation in fat content during foetal life was considerably less than the variation found at any of the later stages of development. The individual difference between the fat contents of the different lobes was up to 2·7 g. %—a difference very small when compared with the difference frequently found in abnormal livers.

Fat Content of Livers after Birth. The fat content of the liver after birth showed a wide range similar to that seen in stillborn infants (Table 4).

While the individual difference in fat content between the left and right livers was not great, there appeared to be a tendency for the right liver to have a slightly higher fat content than the left in infants surviving more than 12 hours.

The livers of lowest fat content, 5-7 g. %, were found in infants dying within six hours of birth.

Discussion

The purpose of this study was to establish some data of the normal water and fat content of the right and left lobes of the liver in the foetus and newborn. Since all of the material studied came from infants who had died, the criteria of normality are arbitrary and based on personal naked eye and microscopic opinion of the livers and of the cause of death of the children concerned.

The criteria used tended to reveal abnormalities of over-hydration and increase in fat content rather than those of the reverse aspect. Fatty vacuolation is easily seen, but there is no similar simple criterion to exclude livers containing abnormally little fat, so we feel that the lower ranges of fat content found were probably from infants with unrecognized general diseases. Also minor differences in the size and staining properties of cells tend to be more obvious when seen adjacently and in the same microscopic preparation. This suggests that selection of cases may have excluded livers showing minor local asymmetrical disease and at the same time admit livers having perhaps a greater generalized deficiency abnormality. For these reasons the ranges of normality can probably be assessed better by general inspection of the figures than by statistical study.

The figures for fat content showed wide variation. If for the reasons enumerated above we ignore the lowest fat levels, i.e., below 7%, and the single liver with fat levels above 18%, there seems to be very little variation in fat content through the whole period studied but the range is over 100%, i.e., from 7 to 15 g. %. This is not surprising as Leathes (1909) noted great variability in the content of the livers of slaughtered animals quite independent of the presence of fatty vacuolation.

Dorkin and Weinberg (1949) found much histologically demonstrable fat in the livers of infants over the weight of 2,425 g. and in infants below 2,000 g. either no fat or an occasional droplet. They concluded that fatty vacuolation in the liver is

normal in the newborn. We do not accept their assumption and this study is concerned only with livers showing no fatty vacuolation. Imrie and Graham (1920) showed that in guinea-pigs the fat content of the liver rose during the latter part of intra-uterine life and fell to normal adult levels within 80 hours of birth. Imrie (1914) had examined the fat contents of the liver in two foetuses showing a fat content of 1·38% (wet weight) at six months' and 2·58% at seven months' gestation. The fat content of two infants dying at 2 days were 1·90 and 3·18%.

Regarding the difference between the left and right lobes of the liver, the technical errors of the method used suggested that a difference of over 1·88 g. % might be significant. The ranges found in each lobe in each age group are very wide, and, as the mean levels in the groups containing the largest number of specimens show differences of no significance, it would seem that there is normally no difference between the fat content of the left and right livers at different stages of maturity. After birth there is no apparent difference in the fat content of the lobes during the first 24 hours, but in infants dying during the rest of the first week there appears to be a tendency for the fat content of the right liver to be higher than the left, the difference between the lobes being up to 5·7 g. %.

Our results indicate at no time a significant difference in water content between the left and right lobes of the liver. In the foetus of nine months' gestation or less the water content ranged from 75 to 80%. In the mature infant it would seem to be approximately 2% less. If the 12 hours following birth are ignored the water content of the liver apparently remains fairly constant between 74% and 78% throughout the neonatal period.

Summary

The fat and water content of the left and right physiological lobes of apparently normal livers has been estimated in stillborn babies and infants dying in the first few weeks after birth.

No difference in water content was found between the left and right lobes either in stillborn babies of different ages after birth. The range of water content up to eight months' gestation is apparently between 75 and 80%. In the mature child and after birth the range is approximately 2% lower.

The fat content of the livers showed a much greater variation than water content, the normal range of fat content being 7-15 g. % dry weight. There appeared to be no significant difference between the fat content of the left and right livers when related to maturity but a tendency for the fat content of the right livers to be higher than the left in infants dying between the ages of 1 hour and 7 days.

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CONGENITAL LOBAR EMPHYSEMA

BY

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Regional obstructive emphysema is not uncommon and is due in most cases to obstruction of a bronchus by secretions, tumour, foreign body or glands. Cohen (1943) described such a condition in association with a bronchial carcinoma and Spivek (1936) mentioned a similar picture in connexion with tuberculous glands. In such cases, however, the obstruction is usually progressive and leads finally to collapse of the affected lobe.

Maxwell (1940) drew attention to the sign, which had been described by Chevalier Jackson, of an expiratory wheeze heard over an emphysematous lobe indicating an incomplete bronchial obstruction, and mentioned a case of a child aged 2½ years who had progressive emphysema which subsided before bronchoscopy could be undertaken.

Little has appeared in the English literature on the subject of lobar emphysema in infancy, the early onset of which suggests a congenital basis. The recent publication of several reports in the American literature of successful lobectomy for obstructive emphysema in infants has made the recognition and treatment of the condition of great interest and importance and suggests that it is more frequent than has hitherto been realized.

The symptoms of the condition are fairly characteristic and consist of increasing attacks of dyspnoea and cyanosis. A history of such attacks calls for a radiograph of the chest which should be repeated a few days later if there is nothing apparent on the first film. The increasing emphysema of the affected lobe will gradually become more obvious both clinically and radiologically.

The purpose of this article is to describe a case of congenital lobar emphysema in a newborn baby, which was also associated with a diaphragmatic abnormality, and to review the papers that have so far been published.

Case Report

J.N., a first child, was born at Whiston County Hospital on December 12, 1951. His birth weight was 7 lb. 6 oz. The delivery was normal and the condition of the baby was satisfactory. No artificial respiration or other resuscitative measures had to be used. Two days after delivery he had a cyanotic attack and examination at that time showed diminished air entry over the right lung suggesting atelectasis. He improved following the administration of oxygen. Six days after delivery, cyanotic attacks recurred and dyspnoea and cyanosis became more constant. Radiographs of the chest showed what appeared to be collapse of the right upper lobe with slight mediastinal displacement to the right. During the next few days the symptoms became more pronounced and gradually the percussion note over the left upper lobe became more and more hyper-resonant and the air entry into the right lung diminished. Further x-ray examination showed an obvious difference from the first film, for now there was a marked herniation of the left upper lobe across the midline leading to compression of the right upper lobe (Fig. 1). It will be noted that at this time there was no evidence of the diaphragmatic hernia which appeared subsequently.

A provisional diagnosis of a congenital cyst of the

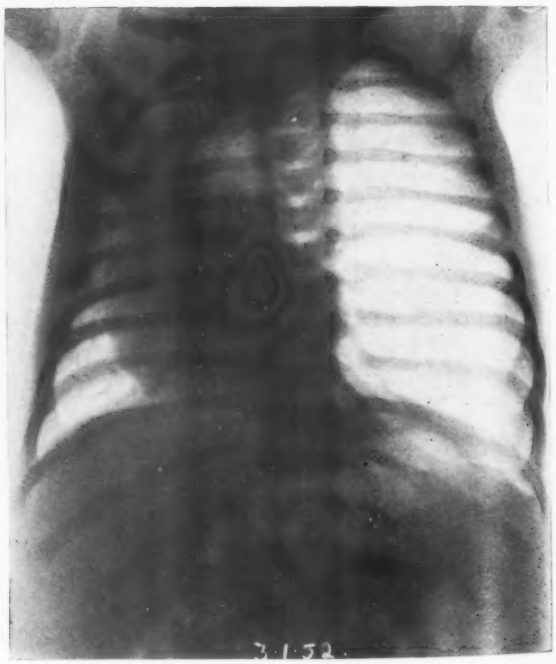

FIG. 1.—Radiograph showing marked emphysema of left upper lobe with herniation across the midline.

lung was made, though some doubt was felt about the accuracy of this as lung markings appeared to be visible and the shadow did not have the circular appearance of a cyst. As the symptoms were by now becoming severe, surgical intervention was clearly indicated and the baby was transferred to the Thoracic Unit at Broadgreen Hospital, where on January 8, 1952, when the infant was 3 weeks old, bronchoscopy was undertaken.

Operative Findings. The infant was anaesthetized with open ether and bronchoscopy carried out. The smallest size bronchoscope was used and the trachea, carina, main bronchi and the opening of the upper lobe bronchi were clearly seen and were normal. There was no flattening and no valvular structure was seen. It was not possible to pass the bronchoscope any further than the opening of the upper lobe bronchi.

It was decided, therefore, to proceed immediately to thoracotomy. Anaesthesia presented something of a problem, as previous experience with congenital cystic disease had shown the dangers of the usual methods employed when the lung is inflated by the anaesthetist's bag. In these cases the cyst continues to expand with each compression of the bag with, as a result, increasing difficulty in oxygenation until the chest is opened and the affected bronchus clamped. In this instance, therefore, a non-cuffed endotracheal tube was used and anaesthesia maintained with nitrous oxide and oxygen only. The left sixth rib was removed and the pleura opened. The upper lobe was voluminous and had the appearance of a pink soufflé. There were no adhesions, although there was a small area of congenital fusion to the lower lobe. The lower lobe itself was foetal in appearance. The change in the upper lobe appeared to affect the whole of the lobe and no normal lung tissue was noted in it. The upper lobe bronchus was clamped and upper lobectomy was carried out by the usual dissection technique. Some air leaked from the raw surface where the two lobes had been fused but in spite of this the lower lobe now expanded to a much greater volume than it had formerly occupied. The chest was closed with drainage.

Post-operatively the infant's condition was far more satisfactory than before operation and it was no longer necessary to administer oxygen. Some air continued to leak from the left lower lobe, however, and after the withdrawal of the tube on the second post-operative day a needle was inserted from which the air still escaped until the sixth post-operative day. At this time the lower lobe was filling more than half the hemithorax. There was no further leakage and the child remained a good colour, feeding well, and in a completely satisfactory condition. Thereafter, successive films showed further expansion of the left lower lobe. On examination of the specimen in the theatre no abnormality whatsoever could be seen in the bronchus which had been divided flush with the left main bronchus leaving no stump.

Pathological Report. An aerated upper lobe showing some emphysematous blebs under the pleura: on section, the lobe contains several emphysematous cysts, the largest of them being about 1 cm. across and there is also moderate diffuse emphysema. Areas of intensified emphysema are present which appear to communicate

FIG. 2.—Section of the left upper lobe showing marked emphysematous changes.

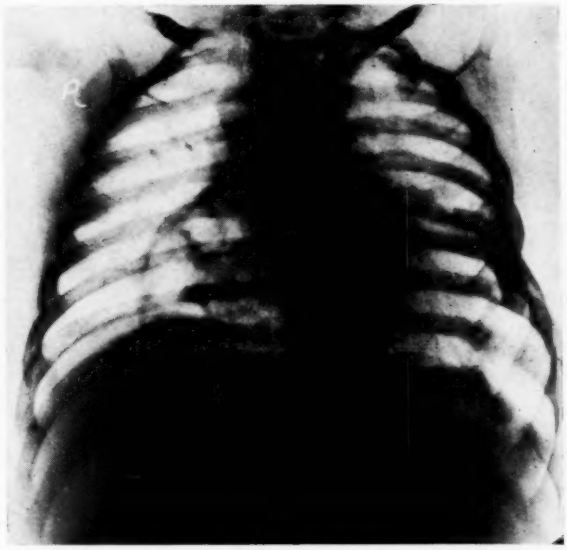

FIG. 3.—Antero-posterior radiograph four months after operation showing the translucent areas at the right base suggesting herniation of the bowel through the diaphragm.

with the hilar connective tissue. No bronchial abnormality was seen but dissection was extremely difficult.

Microscopically there are no inflammatory changes (Fig. 2).

Post-operative Progress. A routine post-operative radiograph showed that the mediastinum had returned to normal, and a further film four months after operation showed a satisfactory state of affairs but now several translucent areas at the right base were visible suggesting herniation of the bowel through the diaphragm (Fig. 3). This was especially obvious in the lateral view (Fig. 4). The baby was thriving, however, and a barium meal was not undertaken until nearly a year after the operation. This confirmed that a fairly large part of the ileum and the mid-transverse colon was herniated through the diaphragm and was lying in the anterior mediastinum (Fig. 5). The baby continues to thrive and now at the age of 2 years has no symptoms referable to the lungs or the alimentary tract. In particular he has no undue liability to respiratory infections. In view of this, surgery for repair of the diaphragmatic defect is being postponed until the child is bigger.

Discussion and Review of the Literature

Isolated cases of emphysema involving one lobe in infants or young children have been reported in the American literature. Caffey (1940) reviewed this condition in association with infection and described seven cases, some of which were relieved by bronchoscopic aspiration of mucus. Overstreet (1939) drew attention to the fact that lobar emphysema could occur due to a congenital defect and he described a case of an infant aged 1 month with obstructive emphysema of the left upper lobe who was found at necropsy to have deficient cartilage rings in the affected bronchus. Shaw (1952) described a case of localized hypertrophic emphysema involving the right middle lobe and another in which the left upper lobe had been affected. He noted that the bronchi to the affected lobes were flaccid. In his discussion he raised the question whether the condition could be due to vigorous artificial respiration, especially high pressure oxygen. This point is interesting in view of the modern use of endotracheal insufflation of oxygen in resuscitating cases of asphyxia neonatorum. Interstitial emphysema and pneumothorax have been known to follow trauma at birth but such emphysema is usually transient and in any event is unlikely to single out one lobe. Shaw

FIG. 4.—Lateral view of Fig. 3 showing the well marked herniation of the bowel.

FIG. 5.—Barium meal, 11 months after birth, showing a large part of the ileum and the mid-transverse colon herniated through the diaphragm.

postulated a chondromalacia of the bronchial tree and noted that in his cases the cartilaginous rings of the bronchi were indeed softer than normal. He assumed therefore that air could enter the lung on inspiration, but during expiration the bronchial walls collapsed due to the weakness of the rings and so retained the air in the distal portion of the lobe affected. A curious feature of this theory appears to be that only one lobe is usually affected by the emphysema. In all the cases reported hitherto lobectomy has lead to a cure without, so far, any recurrence in the other lobes. In a recent publication Sloan (1953), however, quotes four patients who had residual symptoms even after lobectomy and in these the theory of flaccidity of the bronchial tree is reasonable. In two of his cases the left upper lobe was affected and in the other two, the right middle lobe. Lobectomy was successful in each case. The youngest patient was aged 6 days and the oldest 8 months. Each of the lobes showed marked generalized emphysema but no infection and no specific bronchial obstruction was present. In two of the infants there was radiographic evidence of emphysema in other portions of the lung following operation.

Other cases in association with defects of the anterior mediastinum have been reported. Ochsner, De Bakey and Murray (1939) reported a complete absence of the anterior mediastinum visualized at operation for a diaphragmatic hernia in an 18-month-old child but there was no abnormality of the lung. Gross and Lewis (1945) reported an absent anterior mediastinum in a 4-year-old child who was operated on for obstructive emphysema of the right upper lobe caused by absence of the cartilaginous rings in the affected bronchus. The lobe was removed and the anterior mediastinum was reconstructed by suturing the pericardium to the periosteum of the back of the sternum. That a defect in the anterior mediastinum could directly cause lobar emphysema was shown by Lewis and Potts (1951) who reported the case of a 4-month-old boy who had been well until 9 weeks of age when typical symptoms developed. At operation the right middle lobe had herniated through a defect in the anterior mediastinum leading to a kinking of the bronchus and obstructive emphysema of the affected lobe. No definite abnormality of the right middle lobe bronchus could be found.

Williams (1952) reported a case of a 7-month-old infant presenting as asthma. The child was treated as such but finally at the age of 17 months was operated on with a diagnosis of congenital cyst of the lung. At operation a large emphysematous right middle lobe was found but no bronchial abnormality was noted.

Leahy and Butsch (1949) also reported a case involving the left upper lobe in which lobectomy was successful. They also drew attention to the fact that a congenital diaphragmatic hernia itself may be a cause of respiratory distress due to increased pressure on the lungs and mediastinum and that this may necessitate surgical intervention in the neonatal period.

Apart from these isolated cases, no author had produced a series and it seemed therefore that the condition must be rare. However Robertson and James (1951) quoted five cases which had occurred in their practice over a period of two years and suggested that, in fact, the condition might be more common than had hitherto been realized. They found a different set of causes for the bronchial obstruction. In one of their cases a valve-like fold of mucous membrane was demonstrated which apparently allowed air to enter the lobe but, by acting as a valve, impeded the exit. In another case no mucosal fold was demonstrated but the authors suggested that it lay in the stump of the bronchus left behind at operation. In a third case a different reason was postulated, for this time a large vein was found hooked round the right upper lobe bronchus leading to constriction. In a further case a patent ductus arteriosus attached low down on the pulmonary artery was thought to be responsible for the pressure on the bronchus.

Fischer, Potts and Holinger (1952) reported a further series of five cases. In two of these the obstruction was due to a patent ductus arteriosus and in two others to mucosal folds associated with hypoplasia of the bronchial cartilages. In the other case no definite cause was found. Lobectomy was performed with success in every case.

In all the cases reported, with the exception of those of Sloan, complete recovery appears to have been the rule, though if the theory of weakness of the cartilages of the bronchial tree be accepted it is puzzling to know why other lobes are not affected either at the same time or subsequently. Sloan's cases are in marked contrast to all the others in that though they did well in the immediate post-operative period with complete relief of the immediate respiratory embarrassment, the infants seemed more prone to respiratory infections and had more marked symptoms with each attack than would have been anticipated in a normal infant. Sloan suggested that the extra mucus in the bronchi on these occasions was sufficient to increase the obstruction already potentially there due to the flaccid rings. He concluded that it appeared that the whole bronchial tree was involved in the abnormality, and it is interesting to note that Shaw also observed

extreme flaccidity of the whole bronchial tree, though his cases, unlike those of Sloan, had no residual disability.

A curious feature of the condition as a whole is that only the upper lobes or right middle lobe are involved. No cases affecting the lower lobes have been reported. One explanation that has been given is that the lower lobes are more adequately compressed during expiration by the collapse of the thoracic cage and the rising of the diaphragm and that this pressure overcomes any potential obstruction in the lower lobe bronchi. The upper lobes tend to empty more passively.

Robertson and James (1951) reviewed the differential diagnosis, which appears to lie between atelectasis, interstitial emphysema, agenesis, congenital cyst, lobar emphysema secondary to the viscid secretions of bronchitis, foreign body and diaphragmatic hernia pressing on the lung. As they pointed out, in atelectasis there is retraction of the mediastinum with elevation rather than depression of the diaphragm and the atelectatic lung will appear more radio-opaque than the lung compressed by the emphysematous lobe. The lung opposite to the atelectatic lobe never has the ballooned and herniated appearance of the emphysematous lobe. Interstitial emphysema with spontaneous pneumothorax usually has a history of violent respiratory efforts either actively in the form of asthma or passively in the form of pressure anaesthesia. In this connexion it is important to remember the danger of too high an oxygen pressure when an endotracheal tube is passed in the resuscitation of infants suffering from asphyxia neonatorum. Salmon, Forbes and Davenport (1947) reported the necropsy findings of six infants dying shortly after birth with pneumothorax and pulmonary emphysema. There was no bronchial abnormality and the condition was thought to be due to excessive pulmonary ventilation secondary to difficult birth and artificial respiration leading to rupture of the lung alveoli.

In interstitial emphysema, surgical emphysema may be palpable in the neck, and, if the infant survives, the condition is short-lived in contrast to cases of lobar emphysema where the symptoms tend to be progressive.

In agenesis lung markings are completely absent and of course the diaphragm will be elevated on the affected side.

Congenital cysts may present a very difficult differential diagnosis, though in these cases there tends to be a definite ring shadow on radiography. Albert and Potts (1953) have recently mentioned six cases—all emergencies—during a two-year period. They described two of them. The symptoms were very similar to those of lobar emphysema, namely cough, moderately rapid breathing and tendency to cyanosis. The real difference was only apparent at operation. All the patients, the youngest of whom was 5 days old, recovered.

Lobar emphysema secondary to viscid secretions of bronchitis should present no problem, occurring as it does in relation to the infection, but it is well to bear in mind that even in these cases there may be some degree of flaccidity of the bronchial tree as an underlying abnormality.

In the case of foreign bodies, the history and the results of bronchoscopic examination should solve the problem but in any event this accident is unlikely to happen in a young infant unless some thick mucus be aspirated at delivery. It is improbable that such will remain as a plug partially blocking one bronchus—especially an upper lobe bronchus.

A diaphragmatic hernia may cause pulmonary embarrassment by pressure on the lungs but x-ray examination will settle the difference. It is interesting to note that the very large diaphragmatic hernia in our case has never caused any symptoms.

The case which is described here follows the pattern of the others reported though we were unaware of any theories of aetiology at the time of operation and no abnormality of the bronchial tree could be detected but, as the pathologist mentioned, dissection was extremely difficult. The case appears to be distinctive in that there is an associated diaphragmatic defect which has yet to be repaired. No abnormality of the anterior mediastinum was observed at operation, and it is difficult to postulate any direct connexion between the two conditions except on the basis that one congenital defect in the body tends to be associated with another.

Summary

A case of congenital lobar emphysema occurring in a newborn infant is described. A diaphragmatic hernia as an associated defect was also present.

The importance of early recognition of the condition is emphasized as these cases tolerate lobectomy well. The operation is a life-saving measure.

The symptoms are fairly constant and characteristic and it is suggested that when an infant, previously well and with no evidence of infection, has attacks of dyspnoea and cyanosis, congenital lobar emphysema should be considered.

The literature is reviewed and the theories of aetiology mentioned.

We are grateful to Dr. Whitwell for his report on the histology of our case.

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ASPHYXIA NEONATORUM DUE TO A NASOPHARYNGEAL TERATOMA

BY

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Although a nasopharyngeal teratoma occurs but rarely, it may be a cause of acute asphyxia in the newborn baby. The tumour is often readily amenable to surgical removal.

Ehrich (1945) gives a comprehensive survey of the literature relating to teratoid parasites of the mouth. He refers to the earlier publications of Ahlfeld (1875), Arnold (1888) and Schwalbe (1907) and discusses their theories relating to the pathogenesis of such tumours. Ahlfeld believed they were all twin formations. Arnold classified them according to their state of development and agreed that the highly developed variety were true double monsters but believed the more simple type, the so-called hairy polyp, was a tissue malformation due to cell dislocation early in development. Schwalbe favoured a similar classification but considered that all had an identical pathogenesis and were caused by dislocation of germ material. The earlier in development this occurred the more complex was the resulting tumour. At the present time the pathogenesis of teratoma formation is based on the organizer theory of Spemann. Needham (1942) compares naturally occurring and experimentally induced teratomata and concludes that the malformations are only explicable as the result of uncoordinated organizer action. Not only must the liberation of evocator (stimulus) at times and places where it is not normally liberated be considered, but also competence to respond to evocator beyond the time at which it is normally lost. He concludes by stating that primary evocator is present in most adult tissues of animals in the free state and it is therefore likely that prolongation of the period of competence is a more important factor. It is evident that from them both, by all sorts of combinations and permutations, everything that we know of under the name of the teratomata may be produced.

The present report is concerned with the simple type of teratoma or hairy polyp. Ehrich (1945) refers to 79 similar cases and references to 11 more have been found in the literature since that time.

Case Report

D.H. was born on July 3, 1952, the fourth child of a healthy mother. The pregnancy and labour were normal and the birth weight of the infant was 6 lb. 13½ oz. Immediately after delivery a little mucus was removed from the nose and mouth but no significant departure from the normal was noticed.

Three hours later the child suddenly became cyanosed and dyspnoeic. On examination, within a few minutes of the onset of these manifestations, the infant was found to be almost black and there was marked respiratory distress with retraction of the tissues in the submandibular region, suprasternal area and lower part of the chest wall at each attempt at inspiration. The air entry of the lungs was greatly diminished and generalized moist sounds were heard. The mouth was normal but a yellow mass could be seen in the oro-pharynx. As the baby gagged a sausage-shaped tumour was brought forward into the buccal cavity pulling the soft palate anteriorly.

A rubber catheter was passed through the mouth beyond the nasopharyngeal tumour into the pharynx and this immediately provided an efficient airway. Then without anaesthesia the pedicle of the mass was snared and the tumour removed whole. Although the relief from respiratory embarrassment was immediate, clinical evidence of lung atelectasis persisted for a further 48 hours. During this time the baby was nursed in an oxygen tent in the head-down position. A chest radiograph taken on the seventh day of life showed that the lung fields were normal. There was no delay in the establishment of breast feeding and the birth weight had been regained when the infant was discharged from hospital on the fourteenth day of life. A report from the patient's doctor confirms that the child is in good health at the age of 1 year.

A photograph of the teratoma is shown in Fig. 1. The following report on the histology was given by Dr. Gowing:

The specimen is an ovoid nodule measuring 2×1×1 cm. It is apparently covered by skin and there is a narrow pedicle. Examination of the cut surface shows the centre of the nodule to be occupied largely by adipose

tissue. Microscopically there is a small nodule of cartilage at the centre and surrounding this is a broad layer of adipose tissue. The exterior of the nodule is covered by skin which shows well marked keratinization and numerous pilo-sebaceous follicles. The nodule is clearly a congenital malformation and there is no evidence of true neoplasia.

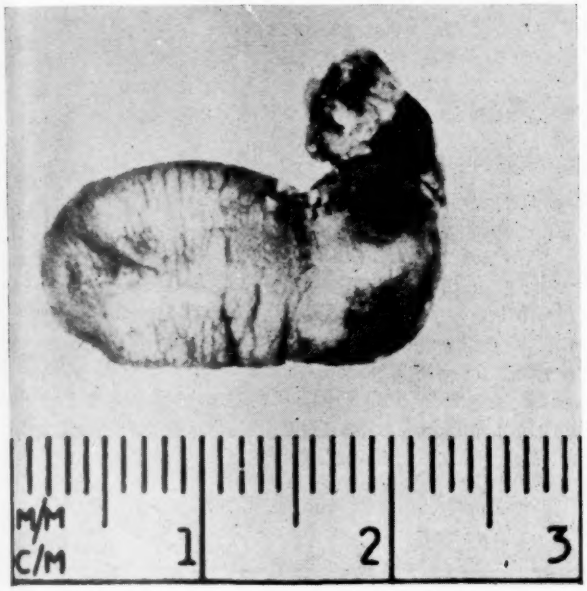

FIG. 1.—Macroscopic appearance of the excised tumour.

Comment

This child was simply and effectively treated surgically within six hours of birth. In the last 20 years six other cases have been recorded where surgical removal of a hairy polyp has been successfully conducted during the neonatal period (Stokoe, 1937; Foster, 1944; Sjövall, 1951; Sala, 1951; Frenkel, 1951; Bodian and White, 1952). The more highly developed teratoma usually occur in stillborn babies but Ochsner and Ayers (1951) describe such a tumour which was removed on the fourth day of life after a preliminary tracheotomy and gastrostomy.

It is interesting that our patient's elder sister, who was one of twins, was admitted to the Victoria Hospital for Children at the age of 20 months with an abdominal tumour. This was a pararenal neoplasm which showed patchy calcification radiologically, and was considered to be a neuroblastoma or teratoma. Laparotomy was performed but the mass was firmly adherent to the vena cava preventing its removal, and its vascularity made biopsy inadvisable. This child is now 4½ years of age and has remained in good health. Although the nature of her neoplasm is so far unproved it is very likely to be a teratoma.

Summary

A case of nasopharyngeal teratoma causing acute asphyxia neonatorum is described. The tumour was successfully removed in the neonatal period.

It is a pleasure to express my indebtedness to Mr. Pereira who operated on this child so successfully. I am grateful to Dr. Ursula James and Mr. Rodney Smith for allowing me access to the case notes of the elder sister.

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A NEUROLOGICAL SYNDROME IN INFANTS RECOVERING FROM MALNUTRITION

BY

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(RECEIVED FOR PUBLICATION JANUARY 26, 1954)

During the past two years, eight infants admitted to this hospital developed neurological disturbances while recovering from malnutrition. These disturbances cleared up partially or completely within several weeks or months of appearance. Summaries of the history and examination of each of the eight infants are given in the accompanying table, but certain aspects of the syndrome are described in greater detail below.

Before the onset of neurological complications these infants were not distinguishable from other severe cases of infantile malnutrition, of which about 500 pass through our wards every year.

The syndrome appeared not while the children were severely ill with malnutrition but some one to eight weeks after dietetic treatment had been instituted and when there was clear evidence of convalescence.

Coarse tremors, Parkinsonian in type, were the earliest and most constant abnormality. They were always fully developed within two to four days of onset. Once they were established, they ceased only

TABLE

ANALYSIS OF CASES

	Case 1	Case 2	Case 3	Case 4
Race (tribe)	Eurafrican	Swazi	Zulu	Zulu
Sex	Male	Male	Male	Male
Age (in months)	13	14	12	12
Month of admission	January	June	February	July
Weight on admission	11¼ lb.	15 lb.	13 lb.	9½ lb.
Manifestations of malnutrition on admission	Atrophic hair, generalized wasting, gross rickets	Atrophic and depigmented hair, oedema, cheilosis, pellagrous dermatosis	Gross rickets, atrophic and depigmented hair	Atrophic and depigmented hair, angular stomatitis, glossitis, pellagrous dermatosis
Duration of diarrhoea before admission	Six weeks	Four weeks	Two weeks	?
Feeds before admission	Proprietary infants' cereal. Occasionally ¼ pint of milk with the cereal preparation, but usually no milk. Sometimes mashed potatoes	Maize porridge without milk three times a day, no milk, or other food containing animal protein, for past 5 months	Soured maize porridge and sugar, no milk	Condensed milk, highly diluted; also oat meal and barley gruels without the addition of milk
Treatment of malnutrition	Altmann formula*	Altmann formula*	Skimmed milk mixture	Altmann formula*
Additional vitamins	Nil	Vitamin B Co., 0·5 ml., on day after admission	Nil	Riboflavin, 5 mg. t.i.d., from 5th day after admission
Interval between change of diet and onset of tremors	27 days	12 days	8 weeks	7 days
Parts affected by tremors	Right arm and leg, tongue and lower jaw	Both arms and right leg	Extremities, head, jaw and tongue	Extremities, head, jaw, tongue and eyelids
Myoclonus	Nil	Both arms and right leg	Extremities	Arms and jaw
Opisthotonus	Present	Nil	Nil	Present
Tendon reflexes	Exaggerated	Exaggerated	Exaggerated	Exaggerated

* Two ounces of dried skimmed milk, 1 oz. of dextri-maltose and one drachm of lactic acid B.P. are dissolved in one pint of water 25 mg. of ascorbic acid which is added to one of the daily feeds, no vitamins, liver extracts or drugs are used in this method of treatment.

during sleep. They involved most commonly and most severely the hands, although one hand was usually affected to a greater extent than the other. All infants except one (No. 8) showed tremors of the lower extremities, but in four cases (Nos. 1, 2, 5 and 6) only one of the legs was involved. In four patients (Nos. 1, 3, 4 and 5) tremors were seen to affect the head, the lower jaw and the tongue in addition to the extremities, and there was also sagging of the jaw and a vacant facial expression. However, neither in these nor in the remaining infants was there any evidence of excessive salivation.

Cogwheel rigidity was always present in extremities showing tremors, but lead pipe rigidity could not always be demonstrated in limbs not affected by tremors.

All of the patients showed disturbances of posture. These manifested themselves usually only in the hands, which were held in a half-closed position, deviated at the wrist towards the ulnar side and with the thumb adducted into the palm (Fig. 1). Only if the tremors were severe were the arms flexed at the elbows. Two patients (Nos. 1 and 4) suffered from opisthotonus for several days after the onset of tremors, and this was associated with marked neck rigidity.

While tremors, cogwheel rigidity and postural abnormalities indicated the existence of an extrapyramidal disorder, there was also evidence of an involvement of other parts of the nervous system. All infants showed grossly exaggerated tendon reflexes, though clonus could never be demonstrated.

FIG. 1.—Case 6 shortly after admission, showing sagging of jaw and the typical posture of upper extremities.

Four patients (Nos. 3, 4, 5 and 7) suffered from myoclonus in the limbs most severely affected by tremors. This occurred usually at the rate of one per second and resulted in a flexion movement of the arm at the elbow or the leg at the knee or hip. Case 5, in which myoclonus was more widespread than in any of the others, will be

OF PRESENT SERIES

Case 5	Case 6	Case 7	Case 8
Xosa	Msutu	Zulu	Zulu
Male	Male	Male	Male
16	22	10	15
August	November	February	March
14 lb.	17 lb.	14¼ lb.	13¼ lb.
Atrophic and depigmented hair, generalized oedema, pellagrous dermatosis, angular stomatitis, glossitis	Sparse, atrophic, black hair, shiny, atrophic skin, oedema of legs	Mild pellagrous dermatosis, sparse, atrophic and depigmented hair, generalized depigmentation of skin	Atrophic black hair, angular stomatitis, some hyperkeratosis of the skin developed in hospital
No diarrhoea according to mother, but diarrhoea on admission	3 weeks	1 week	4 weeks
Proprietary infants' cereal containing 20% of dried skimmed milk	Maize gruel made with water, probably no milk	Proprietary infants' cereal, greatly diluted with water, no milk	Haphazard feeding, proprietary infants' cereal. Total quantity of milk about 12 oz. per day
Altmann formula*	Normal diet for age	Altmnan formula*	Altmann formula*
Nil	Nil	Nil	Nil
12 days	14 days	13 days	27 days
Arms, left foot, jaw and tongue	Arms and right leg	Extremities	Arms only
Left arm and leg, tongue, respiratory and frontalis muscles	Nil	Nil	Nil
Nil	Nil	Nil	Nil
Exaggerated	Exaggerated	Exaggerated	Exaggerated

This mixture is given to malnourished infants in amounts of 2½ oz. per lb. body weight per day, divided into six or more feeds. Except for (Altmann, 1948).

described in greater detail later. The tremors disappeared during sleep, but the jerks caused by the myoclonus could be detected frequently while the child was sleeping soundly. All children with myoclonus sweated profusely.

With the exception of Cases 1, 7 and 8, the infants were unable to carry out voluntary movements with those limbs which were trembling most severely. In Cases 2, 4 and 5 voluntary movements were confined to head and eyes while the neurological complications were at their height.

Irritability is a feature of infants suffering from malnutrition, and all eight cases were irritable before the tremors started. However, there was no doubt that the irritability increased when the tremors began.

One case (No. 5) was confused for 24 hours during an attack of aspiration bronchopneumonia, but this was doubtless due to cerebral anoxia, because none of the other children showed any clouding of consciousness, and this particular child improved rapidly when the air-way was cleared and oxygen was administered. These children were usually more wakeful than others of their age, and two cases (Nos. 2 and 5) suffered from severe insomnia and were hardly ever seen asleep until sedated with 3 grains of phenobarbitone per day.

Further Course of the Neurological Disorder

In Case 1 death occurred before there was any change in the nervous manifestations, and was due to gastro-enteritis. The other patients improved gradually. If myoclonus or opisthotonus were present, these were the first to disappear, and they did so always within one or two weeks of onset. The tremors left the legs several weeks before a similar improvement was noticed in the upper extremities. Tremors could sometimes be felt in the fingers for some weeks after all visible evidence had gone. Voluntary movements returned before tremors had ceased. In the case of the hands, they appeared first in the thumb and index finger, and the children were seen to play with these fingers while the others were still flexed inactively into the palm.

The neurological disturbances did not relapse, once they had begun to regress. In Cases 2, 7 and 8 the patients left hospital without any abnormal neurological signs, except brisk reflexes. In Case 4 there were still tremors and rigidity of the left arm and a tremor of the tongue when the child was discharged from hospital four months after the start of the syndrome. Unfortunately, he failed to attend the out-patient department after discharge. However, when he was re-admitted to hospital six months later with bronchopneumonia, examination of the nervous system was normal except for abnormally brisk reflexes. One child (Case 6) is still under observation as an out-patient, some eight months after the start of tremors. He still has a Parkinsonian facies (Fig. 2), his gait is shuffling, his left arm shows lead pipe rigidity and his tendon reflexes are abnormally brisk. However, he no longer suffers from tremors and he is normal mentally. Two other patients (Nos. 3 and 5) had remains of tremors and cogwheel rigidity on discharge from hospital. Their further progress could not be observed because the parents did not bring them to the out-patient department, and they could not be traced at their former addresses. Thus, apart from the one patient who died, all infants recovered almost completely from the syndrome.

FIG. 2.—Case 6 seen 8 months later. His jaw is still sagging, but his posture is almost normal. The Harrison's sulcus was present on admission, but there was no evidence of active rickets.

Results of Investigations

Serological tests for syphilis were negative. Mantoux tests in strengths of 1 in 1,000 and 1 in 100 were also negative. Two children had clinical evidence of rickets and the bones showed evidence of it on x-ray examination. Although all eight infants were suffering from diarrhoea before the onset of tremors, pathogenic bacteria were demonstrated only in the stools of Case 8, which yielded a growth of *S. flexner*. The serum in Case 3 agglutinated *S. flexner* in a significant titre of 1 in 256. Diarrhoeal stools are almost the rule in cases of infantile malnutrition in this country, but pathogenic bacteria are not responsible for these (Kahn and Robertson, 1952). It is, therefore, assumed that the diarrhoea in the remaining six infants was not attributable to intestinal infection with bacteria, but that it was caused by the underlying nutritional disorder.

In malnourished infants seen at this hospital the liver function tests are usually abnormal, and they

remain so for some time during convalescence. In several of the cases liver function tests were markedly abnormal. However, in Case 8 the thymol flocculation and turbidity, Takata-Ara and colloidal red tests were normal when tremors began, although mild liver dysfunction was suggested by an albumin/globulin ratio of 3·4:3·3. Needle biopsies of the liver were carried out on Cases 4 and 5. No structural abnormalities could be detected in these specimens, apart from mild fatty changes.

The urine of three of the infants (Nos. 4, 5 and 6) was examined by paper chromatography for abnormal excretion of amino-acids. No such abnormalities were detected.

Only in Case 3 did lumbar puncture show any abnormal findings. On the fourth day after the onset of tremors the cerebrospinal fluid contained 18 polymorphonuclear leucocytes and 8 lymphocytes per c.mm., with total protein 76 mg. per 100 ml., glucose 63 mg. per 100 ml., and chlorides 721 mg. per 100 ml. Six days later the cerebrospinal fluid did not contain any cells and the protein content was 46 mg. per 100 ml.

Electro-encephalograms were carried out on Cases 4, 5 and 6. They show scattered areas of abnormal electrical activity, but discharge phenomena were not seen.

Post-mortem Findings

Only one patient (No. 1) died, death being due to gastro-enteritis of unknown aetiology which was contracted in hospital one month after the onset of tremors. Post-mortem examination was carried out 48 hours after death. Unfortunately, the significance of the case was not realized at the time and only a few parts of the brain were taken for microscopic examination. They were reported on as follows:

'Section of the meninges over the region of the central sulcus shows slight oedema. The underlying brain is congested and there is well marked interstitial and perivascular oedema. Around an occasional vessel there is recent extravasation of blood cells into the perivascular spaces. Similar, less marked, changes are noted in the cortex from the region of the Sylvian fissure.

The basal ganglia and the internal capsule show congestion and interstitial and perivascular oedema. The nerve cells show post-mortem autolysis, but no other definite degenerative lesions. Sections from the mid-brain and medulla, including the olive, show no significant pathological lesions, apart from congestion and interstitial and perivascular oedema.'

The cerebral sinuses did not reveal any signs of thrombosis. The lungs showed evidence of terminal bronchopneumonia, and there were mild fatty changes in the liver. No other abnormalities were detected.

(In the assessment of the post-mortem findings of the brain it should be kept in mind that any or all of the abnormalities described may have been caused by the fatal attack of gastro-enteritis.)

Detailed Case Reports

The case reports of No. 5 and No. 7 are presented in greater detail, the first as an example of a severe and the second as an example of a mild variant of the condition.

Case 5. A boy (Xosa), aged 16 months, was admitted to hospital on August 16, 1952, with the diagnosis of 'nutritional oedema'. The child weighed only 14 lb. There was generalized pitting oedema. Other evidence of malnutrition was provided by severe pellagrous dermatosis, depigmentation of hair and skin, glossitis and angular stomatitis.

The mother stated that the child had been fed artificially since birth. For 10 months before admission feeds had been prepared from a proprietary infant food which consists of maize (50%), dried skimmed milk (20%) and a mixture of cereals other than maize (30%). This had been mixed haphazardly with water, instead of milk, and had been administered to the infant whenever he cried.

In hospital the child received the standard Altmann formula without additional vitamins. For the period August 18-22, he was kept on a metabolic bed for balance studies, and an accurate note was taken of his clinical condition. It is certain that during this time there were no unusual nervous manifestations, apart from the irritability which is commonly associated with infantile malnutrition. On August 26 and 27, the patient's condition was greatly improved, his irritability had lessened, and he had begun to play with his toys. On August 28, 12 days after admission to hospital, severe tremors were noticed in the left arm. However, the child was still using both his hands while playing. On the following day the tremors were also noted in the left foot and the right arm, and these limbs showed cogwheel rigidity. The condition remained unchanged the following day, but on August 30 profound deterioration had set in. All four extremities were affected by tremors and cogwheel rigidity. Voluntary movements, except those of the eyes and the head, had ceased. Severe myoclonus was producing a one per second flexion of the left arm and the left leg. The tongue showed a fine tremor and, in addition, myoclonic jerking at a rate of two per second. Myoclonus was also detectable in the frontalis muscles, the sternomastoids and the respiratory muscles, the latter causing jerkiness of respiration. The child appeared to be unable to swallow, and mucus was collecting in the throat. Examination of the chest indicated the presence of bronchopneumonia. The patient was cyanosed, his consciousness was clouded and he was sweating profusely.

During the following four days the child was fed nasally, mucus was aspirated from the nasopharynx, and the pneumonia was treated with penicillin and oxygen. Under this treatment the cyanosis disappeared, consciousness returned to normal, and the clinical signs of bronchopneumonia cleared up. At this stage it was realized that the patient had hardly ever slept since the onset of the tremors and that he was usually looking around anxiously. He was, therefore, given 3 grains of phenobarbitone per day. Thereafter he slept for longer periods, but did not close his eyes during sleep.

The nervous manifestations showed definite signs of abating nine days after they had begun. The myoclonus disappeared, and the legs were no longer affected by tremors. Seven weeks later the child began to smile and to take notice of his surroundings. A few days after this he was able to sit upright. However, the tongue and the hands were still trembling, the face bore a mask-like expression and the lower jaw was sagging. Twelve days after sitting up the child began to crawl, but was unable to use his left hand in doing so.

The tendon reflexes were abnormally brisk from the day neurological complications had first been seen until the patient left hospital four months later. On discharge the patient's left hand was still affected by tremors and cogwheel rigidity; he was not using his left hand when crawling: his lower jaw was sagging and his tongue was trembling occasionally.

The parents did not attend the out-patient department with the patient after discharge, and attempts to locate the infant at home were unsuccessful.

Case 7. A boy (Zulu), aged 10 months, was admitted to this hospital on February 20, 1953, with the diagnosis of malnutrition and early bronchopneumonia.

The diagnosis of bronchopneumonia was confirmed by x-ray examination and the abnormal chest signs resolved within one week under treatment with penicillin and sulphonamides.

The diagnosis of malnutrition was based on mild pellagrous dermatosis over the forehead and extensor surfaces of the legs, atrophic scalp hair and depigmentation of the parts of the body not affected by the dermatosis. The child was a little underweight at 14¼ lb.

He had been under the care of his grandmother for several months. She had fed him on a proprietary infant cereal which does not contain milk. This had been cooked with water, and not with milk as recommended by the manufacturers. The child had not received any milk or other food while living with his grandmother.

In hospital the malnutrition responded readily to the Altmann formula, but 13 days after admission coarse tremors were noticed in the left hand. The following day tremors affected all four extremities, and these were also the seat of cogwheel rigidity and myoclonus. However, no abnormalities were seen elsewhere in the body, the child was only mildly irritable, and he was able to carry out voluntary movements. All tendon reflexes were abnormally brisk and the child was unable to sit up unsupported.

The myoclonus disappeared entirely in four days. Ten days later the tremors had diminished in intensity, except those of the left hand, and the child was able to sit up unsupported. All tremors ceased 20 days after they had first been noticed. The briskness of the reflexes, however, remained unchanged.

Discussion

Severe infantile malnutrition is common in the non-European community of South Africa. It is usually caused by a cereal diet to which little or no milk has been added. The common manifestations of the deficiency state resulting from such a diet have been described in articles dealing with infantile pellagra, malignant malnutrition and kwashiorkor. Advanced cases suffer from retardation of growth, oedema, pellagrous dermatosis, mucosal lesions, atrophy of the scalp hair, depigmentation of the skin and scalp hair, diarrhoea, hypo-albuminaemia and fatty liver. However, neurological disturbances are not a feature of infantile malnutrition in South Africa, with the notable exception of the irritability to which reference was made above.

It might, therefore, be thought that the association of the condition just described with infantile malnutrition was a fortuitous one. This is not likely to be the case, even though its incidence was less than 1% of all cases of malnutrition admitted to hospital, because (1) this syndrome has not been observed among tens of thousands of children who attended this department for conditions other than malnutrition, and (2) the syndrome developed in our cases at a specific time, namely, during convalescence from malnutrition.

We must now explain why the condition has not been noted by others who see large numbers of malnourished infants. Suspicion falls on environmental factors and the dietetic management of infantile malnutrition practised at this hospital.

It is known that extrapyramidal nervous lesions, such as described above, can be caused by carbon monoxide, manganese, nitrous oxide, carbon disulphide, potassium cyanide and barbiturates. None of the eight children were in contact with these substances before the onset of tremors. Contamination of the feeds in hospital can be ruled out, because in Case 3 the tremors developed while the child was under treatment with skimmed milk at home, and in Case 6 symptoms occurred when the patient returned to a better diet at home after boarding in the country with his grandmother who had fed him on cereals until he began to suffer from nutritional oedema.

The eight infants were not suffering from a post-encephalitic syndrome because (1) not one of them

showed abnormal neurological signs before the onset of tremors; (2) they did not show clouding of consciousness either before or after admission to hospital (except Case 5, during anoxia caused by bronchopneumonia); (3) the seven survivors recovered from the syndrome, either completely or partially, in a matter of weeks or months, whereas the neurological damage of encephalitis is usually permanent.

Severe liver disease may be combined with nervous manifestations such as those described above. Hepato-lenticular degeneration is an example of this association, but tremors, cogwheel and lead pipe rigidity and myoclonus occur also in acute and subacute necrosis of the liver (Walshe, 1951). However, the liver in Case 1, where death was due to an intercurrent illness, showed no abnormalities, except mild fatty changes. The same applies to the needle biopsies of the livers of Cases 4 and 5. Furthermore, flocculation tests for liver function carried out in Case 8 were normal when tremors began. We can, therefore, state with some assurance that severe liver damage played no part in the pathogenesis of the syndrome.

Disorders of the extrapyramidal nervous system have been observed in pellagrins (Belmondo, 1889; Lewy, Spies and Aring, 1940). There is no fundamental difference between pellagra and what is commonly called infantile pellagra, malignant malnutrition, kwashiorkor or infantile malnutrition. Both adult and infantile deficiency states are caused by a diet which lacks animal protein and which is composed largely, if not entirely, of food of vegetable origin. In adults the consumption of this diet results in a disease in which signs of vitamin B deficiency predominate. In the quickly growing child signs of protein deficiency are prominent and often overshadow those of vitamin deficiencies.

This multiple deficiency state is treated at this hospital with the Altmann formula. As stated before, vitamins or other additions are not employed. This regimen assures an adequate supply of protein of high quality, but its vitamin content is unknown and may be inadequate under certain circumstances. It is important to recall that the two children who developed tremors before admission to hospital also received a diet with a satisfactory protein content but no additional vitamins.

The repair of the state of malnutrition depends not only on an adequate intake of protein of high quality, but also on the availability of other essential components of the food. If there is a deficiency of the latter, the process of repair may be expected to proceed in a disorderly fashion. It is suggested that the syndrome described above may be a manifestation of such an imbalanced recovery, caused by a diet rich in protein but deficient in other essential factors.

The nature of these missing factors is yet unknown. Lewy *et al.* (1940) state that Bean and Spies obtained some dramatic recoveries from the Parkinsonism of pellagra when patients were treated with vitamin B6 (pyridoxin hydrochloride). This vitamin was given to two of our patients when they were suffering from the neurological complications (Cases 5 and 8). Both these patients improved gradually, but it is doubtful whether improvement was appreciably speeded up by this vitamin.

Summary and Conclusions

Among 1,000 cases of infantile malnutrition admitted to Baragwanath Hospital there were eight with characteristic neurological disturbances. These consisted of tremors, similar to those seen in Parkinsonism, cogwheel rigidity and lead pipe rigidity of the extremities and exaggerated tendon reflexes. Some infants also showed myoclonus, opisthotonus and insomnia. These manifestations developed at a time when there were already signs that the nutritional state of the patients was improving. The syndrome disappeared entirely, or nearly so, within a few weeks or months of onset.

It is suggested, albeit on slender evidence, that the syndrome was the result of an imbalanced therapeutic regimen.

I am indebted to Mr. H. D. Barnes for the chromatographic analysis of the urines, to Mr. D. Gamsu for the electroencephalograms and to Dr. J. Higginson for the post-mortem examination and the reports on the liver biopsies.

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INTESTINAL OBSTRUCTION AS A LATE COMPLICATION OF FIBROCYSTIC DISEASE OF THE PANCREAS (MUCOSIS)

BY

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The features of fibrocystic disease of the pancreas are well recognized following the description by Andersen in 1938 of three main clinical forms.

The first is that of intestinal obstruction in the first few days of life due to meconium ileus. About a fifth of all cases present with failure to pass meconium which is followed by vomiting and abdominal distension. It results from inspissation of meconium in the small bowel and at operation or necropsy the upper part of the small bowel is seen to be distended with gas and fluid. The lower part is filled with hard inspissated meconium and the bowel wall hypertrophies and tapers into an unexpanded ribbon-like colon. Perforation of the bowel wall may occur causing meconium peritonitis while volvulus and sometimes atresia of the small bowel may result. Bodian (1952) describes three instances of meconium retention in which spontaneous recovery occurred a few days after birth although all finally succumbed to the disease.

The second form is that of respiratory disorders which is marked by a distressingly persistent and spasmodic cough which simulates pertussis and is associated with episodes of respiratory infection usually due to *Staphylococcus aureus*. Respiratory distress with an increased respiratory rate, signs of infection and emphysema may be noted. Bronchiectatic changes are common and finger clubbing and even cor pulmonale may develop.

The third form is that of the coeliac syndrome in which failure to thrive in spite of an excellent appetite is followed by loose offensive stools, gaseous abdominal distension, wasting and stunting.

Meconium ileus is usually fatal though immediate survival has followed surgical intervention but later features of the disease soon supervene. Numerous variations and combinations of symptoms may confuse the clinical picture but, despite fluctuations, the course of the disease is invariably fatal.

In fibrocystic disease of the pancreas, intestinal obstruction after the neonatal period due to inspissated small bowel contents with recovery is considered worth while reporting.

Case Report

John C. was first admitted to hospital on December 8, 1951, aged 13 months, with a persistent cough and failure to thrive. Birth weight was 6 lb. and after two months of breast feeding, dried milk and later raw cow's milk feeds were substituted. At 3 months a spasmodic but persistent cough resembling pertussis developed. At 6 months mixed feeding was started, and in spite of an excellent appetite the child did not thrive, having loose, offensive and frequent stools.

Of the family, the parents and three brothers are alive and well, two sisters and a brother died at 2 months, 6 months and 4 months; each child failed to thrive and developed loose, offensive stools and a cough like that of pertussis which led to a terminal respiratory illness.

On examination, the child was marasmic, weighing 12½ lb., with abdominal distension and a loose cough associated with scattered rhonchi in the chest. Investigation showed no tryptic activity in the stools or in three specimens of duodenal juice. The Mantoux reaction was negative. *Staphylococcus aureus* was cultured from the nasopharynx and a radiograph of the chest showed emphysema and heavy hilar shadows. Treatment with aureomycin and pancreatin resulted in marked improvement and a gain of 2 lb. in weight in 3 weeks. The child was discharged on January 4, 1952, on a high-protein diet with pancreatin granules, 45 gr., before each feed and aureomycin, 250 mg. daily.

Progress was satisfactory until February 4, 1952, when the supply of pancreatin ran out and could not be replenished. The next day the child vomited and later developed abdominal pain. On February 9, when readmitted to hospital aged 15 months, vomiting was continuous and, except for one small stool two days before, constipation was complete.

The child was irritable with bouts of abdominal pain causing the legs to be drawn up on to the abdomen. The latter was grossly distended but resonant. Bowel

sounds but no visible peristalsis were present. An indefinite mass was present in the right iliac fossa, the rectum was empty and no blood or mucus was present or had been passed.

Acute intestinal obstruction was diagnosed and immediate laparotomy undertaken. On opening the peritoneal cavity a small amount of clear fluid was seen; the whole of the small bowel was found to be intermittently obstructed by masses of putty-like material in the bowel lumen. It was so firm that it could not be expressed through the ileocaecal valve. The large bowel was unobstructed. A portion of the small bowel was packed off and an incision made through the bowel wall; from the lumen a tenacious material like liquid rubber was extracted. The incision was repaired and as the whole of the small bowel was affected no further operative procedure was undertaken.

Post-operatively hydration was maintained by intravenous and subcutaneous fluids. After gastric aspiration 45 gr. of pancreatin granules freshly dissolved in a small quantity of water were given at four-hourly intervals. A daily bowel wash-out was given and on February 16 a large bowel action followed with relief of abdominal distension and vomiting.

From February 14, terramycin, 50 mg., was given orally twice a day. The child made an uninterrupted recovery and was discharged to continue on a high-protein diet with pancreatin 45 gr. before each feed. On July 21, 1952, the child was again admitted with a further respiratory infection which responded to aureomycin therapy. Investigations again confirmed the lack of tryptic activity in stools and duodenal juice.

Discussion

This child's illness illustrates the customary course of fibrocystic disease of the pancreas with the early onset of respiratory and alimentary symptoms. The family history suggests that three siblings suffered from the same disease which is known to be inherited as a recessive characteristic. The diagnosis was confirmed by the lack of tryptic activity in the stools and duodenal juice on repeated examinations. The development of intestinal obstruction due to inspissated small bowel material has been reported only once before as a late complication in fibrocystic disease of the pancreas.

Levy (1951) records such an instance in a child at 7 months of age. Fibrocystic disease of the pancreas had been diagnosed at 9 weeks and treated with pancreatin, 60 gr. daily. When acute intestinal obstruction developed a tentative diagnosis of intussusception was made and laparotomy performed. The small bowel was found to be distended and plum-coloured, with haemorrhages in the root of the mesentery; the colon was empty and contracted. No surgical procedure was undertaken and the child died the following day. At necropsy in addition to the laparotomy findings, the small bowel was filled with putty-like material. There was no evidence of volvulus, intussusception or any other organic obstruction present. The pancreas was firmer than normal and showed histologically the features characteristic of fibrocystic disease with a great increase in fibrous tissue, cystic dilatation of the ducts which contained desquamated epithelium and homogeneous eosinophilic tissue.

These two cases closely parallel those of meconium ileus with the inspissated gut contents causing intestinal obstruction which affects the small bowel leaving the large bowel collapsed but unobstructed. In meconium ileus the primary cause of obstruction is the abnormal physical character of the meconium, suggested by Landsteiner as early as 1905 to be due to lack of pancreatic ferments. It may be followed by volvulus and may lead, according to Lelong, Petit, Le Tan Vinh and Borniche (1950), to secondary atresia of the small bowel. In fibrocystic disease of the pancreas the degree of involvement of the pancreas and its ability to secrete pancreatic ferments must influence the manifestations of the disease; absence of secretion in the late intra-uterine period may lead to meconium ileus, partial lack to meconium retention, while deficient secretion in infancy may result in the coeliac syndrome or obstruction due to inspissation of bowel contents as in these cases.

It should be noted that vomiting unassociated with coughing, which is not an uncommon symptom of this disease, may be due to such an abnormality of small bowel contents. This is supported by the report of Rasor and Stevenson (1941) of a boy suffering from fibrocystic disease of the pancreas in whom vomiting was a persistent feature. At post-mortem examination at 1 year of age, the intestinal contents were found to be of a putty-like consistency. As Levy (1951) suggests, the younger and more debilitated children are liable to this form of intestinal obstruction as older children with their more powerful intestinal peristalsis can probably propel the abnormal faeces through the ileocaecal valve.

In the case reported the intestinal obstruction followed closely the cessation of pancreatin therapy and was possibly relieved by the oral administration of pancreatin. This suggests a further use for pancreatin which has been advocated by Andersen (1945) as a form of replacement therapy. Newer preparations of enteric-coated pancreatin granules of three times the strength of the B.P. preparation are fairly well tolerated and effective in improving the absorption of food as well as the consistency and odour of the stools.

The occurrence of intestinal obstruction as a late

complication of fibrocystic disease of the pancreas must be fully recognized. Laparotomy will confirm the obstruction is due to inspissation of small bowel contents and an ileostomy should be performed because the site of maximal obstruction is in the region of the ileocaecal valve and as this procedure has proved successful in cases of meconium ileus reported by Bodian (1952) and Hiatt and Wilson (1948). By this route, freshly prepared pancreatin can be irrigated into the small bowel while pancreatin is also given by gastric tube after aspiration. By these means, the abnormal bowel contents may be softened and liquefied thus relieving the intestinal obstruction.

Summary

A case of intestinal obstruction due to inspissated small bowel contents at 15 months of age is reported. Occurring as a late complication of fibrocystic disease of the pancreas the similarity to meconium ileus is discussed. Attention is drawn to the condition which is best treated by ileostomy and pancreatin therapy.

I am grateful to Dr. A. A. H. Gailey and Mr. Ian Fraser for permission to publish this case.

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BOOK REVIEWS

Précis de Génétique Médicale. By MAURICE Lamy. (Pp. 256; 108 figures and 38 tables. Fr. Frs. 1,800.). Paris: G. Doin. 1952.

The advances in medical genetics in the past 10 years have made it necessary for Professor Lamy to write a new book rather than a third edition of his earlier book. Once again he has given an admirably clear and complete account of those aspects of human genetics which are of interest to the medical practitioner in little over 200 pages. In particular the mathematical side of the subject is simply and lucidly explained. Simple Mendelism, variability in gene manifestation, polyfactorial inheritance, mutation and eugenics are all discussed. There is also a chapter giving a brief panaroma of the genetics of disease and, at the end, a brief account of statistics.

Anyone who has the courage to write a book on a subject which is at an early stage of development lays himself open to criticism. The chapter on mutation would be better perhaps earlier in the book and should have been given greater emphasis; it is the constant tendency of germ-plasm to deteriorate by mutation, at times producing a recognizable disease, at times perhaps a mere reduction in vitality, that makes human genetics more than an academic exercise. The old survey on which the gloomy prognosis for the children of cousin marriages is based should not have been quoted. Although no more acceptable survey is available, it is surely a matter of common experience that the proportion of defective children in such marriages is not as high as 30%. The English reader will be startled to see eugenics discussed in terms of sterilization and advice against marriage, with no mention of the more practical method of achieving differences in fertility by voluntary family planning. The graphs showing the effect produced on the frequency of dominant recessive disorders, if those who possessed them did not reproduce, are more useful if read backwards. If a disease is at all serious natural selection is already keeping its incidence somewhere near the limit set by the mutation rate. But read backwards the charts show the rate at which the disease will increase in frequency if natural selection is reduced by an effective treatment and no artificial selection is substituted; it is this aspect which will be important practically.

The references contain some surprising omissions, such as that of Dukes on the inheritance of multiple intestinal polyposis and of Fogh-Andersen on hare-lip and cleft palate.

These criticisms are, however, all on matters of opinion and emphasis rather than fact. Professor Lamy acknowledges his debt to the books of Roberts and Stern, but the medical practitioner who reads French fluently will probably find this book an easier introduction than any written in English.

When the book is reprinted the undue numbers of misprints should be corrected; besides the listed errata, these include two pedigrees printed upside down and a remarkable Teutonic spelling of the surname Fisher and the town of Shrewsbury.

Chirurgie du Nouveau-né et du Nourrisson. By BERNARD DUHAMEL. (Pp. 308; 158 figures. Fr. Frs. 1,920.) Paris: Masson et Cie. 1953.

Some of the chapters were written for a book by the late Professor Leveuf and had been approved by him, while his successor, Professor Fèvre has contributed the foreword. The book, therefore, gives an account of the practice of the infant surgical clinic of the Hôpital des Enfants Malades (Paris) and for that reason alone is worthy of study. In the introductory chapters the author discusses the pre- and post-operative care of the young infant and the methods of anaesthesia, and rightly emphasizes the need for the development of special centres for this type of surgery.

In the next section, under the heading 'asphyxial syndromes and disorders of deglutition', the author includes sections on oesophageal atresia and postero-lateral diaphragmatic hernia. The next section, on congenital occlusions of the alimentary tract, also follows the usual teaching of to-day. The classification of ano-rectal atresias and fistulae does not seem to be an improvement on that of Ladd and Gross, but the advocacy of the more frequent use of abdomino-perineal procedures conform with the views of many paediatric surgeons in this country.

The modern interest in hiatus hernia is shown by this section, occupying 28 pages in comparison with the eight pages allocated to pyloric stenosis.

In the treatment of acute intussusception, Duhamel prefers to employ barium enema under general anaesthesia, but he admits that proof of reduction cannot be obtained and, therefore, reduction is confirmed by a small incision in the right iliac fossa. It is illogical to compare the mortality rate of those reduced by enema and those reduced at operation when barium enema has already failed. It is unlikely that many British surgeons will be converted to this method of barium enema reduction, which failed in 60% of the patients treated by this means.

These are minor criticisms and the book should be of interest to all who are interested in the surgery of infancy because it is a frank account of the author's own experience as well as that of the clinics in which he works. Some

of the line drawings lack clarity but the radiographs are well reproduced and well chosen.

Advances in Pediatrics, Volume VI. Edited by S. Z. LEVINE. (Pp. 323; 58s.;$7.00.) Chicago: The Year Book Publishers. Distributed in Great Britain by Interscience Publishers, Ltd. 1953.

It is as much a pleasure to welcome the sixth volume of this well-known series as its forerunners. It contains seven monographs by acknowledged authorities and each section can be taken as an up-to-the-minute summary of its subject.

The subjects dealt with in this volume are lymphosarcoma in childhood, an interesting excursion into preventive pre-natal paediatrics, intestinal obstruction in the neonatal period, haemolytic disease of the newborn, pulmonary pathology in the newborn, the lipoidoses and megaloblastic anaemia of infancy. On each of these widely divergent topics the same high standard of thoroughness and clarity is maintained and no one could fail to read any of the sections with interest and profit. If one note of regret may be sounded it is that whereas in Volume V three of the six monographs were from Europe, in Volume VI only one out of seven is not a United States product. It is to be hoped that in future volumes of this valuable series a better geographical balance may obtain.

Pédiatrie. By ROBERT DEBRÉ and MARCEL LELONG, with the collaboration of STEPHANIE THIEFFRY and JEAN RIVRON and 36 others, 2 vols. (Pp. 2,234; Fr. Frs. 14,500.) Paris: Les Editions Médicales Flammarion. 1952.

This monumental work appears as one part of the 'collection medico-chirurgicale à revision annuelle' under the general direction of Professor Pasteur Vallery-Radot, and the loose-leaf system has been adopted. It will be realized that the production of a system of paediatrics within the framework of a complete system of medicine in which separate volumes are devoted, for instance, to infectious diseases, dermatology and the various organs, is an undertaking of the first magnitude. Not only have the contributions of some 40 authors to be fused into a composite whole in so far as it is possible to distil 'une âme, une mémoire, une pensée collective' from 40 paediatricians, but a watchful eye must be kept on other volumes in the larger series to avoid unnecessary repetition. In this formidable task Professors Debré and Lelong have been singularly successful, and the product of their labours is a scholarly and dignified work of reference which should prove a major landmark in the French paediatric literature. Admittedly some of the sections, for example, the one devoted to coprology, are reminiscent of an earlier epoch of paediatrics, when the physician would be accompanied on his ward round by a trolley containing specimens of every patient's stool, but it is perhaps a wholesome reminder that the doctor of today should still use all his faculties including his sense of smell. The arrangement of the sections is also in some cases a little puzzling. Thus elementary generalizations on congenital diseases are followed by a section devoted to heat, cold, air and sun, and this in turn by a consideration of the allergic constitution. A short bibliography is appended to each section, and it may be felt that rather more references might usefully have been given in a work of this magnitude. Apart from these minor criticisms, however, the authors are to be congratulated on both the scope and content of these volumes. The illustrations are well chosen and well produced, though not profuse, and where radiographs of the chest are included, the admirable practice of appending a line diagram has been followed.

Child Psychotherapy. By S. R. Slavson. (Pp. 332; 30s.) Oxford University Press (London: Geoffrey Cumberlege). 1953.

Too few books have been written about the practice of psychotherapy for children, perhaps because of the rapid changes in technique which have developed in the last few years; perhaps also because psychotherapy with children must, to some extent, remain a personal relationship with a highly individual quality which is difficult to convey to a reader.

Among the newer techniques are those of group work, largely pioneered by the author of the work under review. For this reason it is disappointing that he devotes half the book to theories which are largely derived by him from Freudian analytic concepts. In places their description lacks the clarity of the original, and the tendency to introduce new terminology seems to add to this confusion.

It would have been of great value to learn more of the actual techniques of group therapy, although the author gives many references to others of his own works in this field. We are told that groups are made up of some children who are reckoned to be neutral within the group, while others are (p. 282) 'selected for the role of instigator in groups'. But we are not told how such selection is made, nor by whom.

It is evident that group therapy is not *faute de mieux* a way of dealing with a lengthy waiting list. It is a method of choice in certain cases, and one which places a high value on both the diagnostic and the therapeutic possibilities of social interaction. In spite of the neutral attitude so essential in the therapist, it is perhaps evident that the author is himself a vigorous and dynamic personality, and that his methods are particularly difficult to convey in a verbal account.

A Handbook on Diseases of Children. 7th edition. By BRUCE WILLIAMSON. (Pp. 467; 103 figures. 21s.) Edinburgh and London: E. & S. Livingstone. 1953.

The appearance of the seventh edition of this handbook only two years after the publication of the sixth, shows what a large demand there is for a textbook of paediatrics not too expensive for the student's pocket, and almost small enough to go in it.

Antibiotics and Children's Diseases. (Pp. 298; illustrated. £3 3s.) Distributed for Le Centre International de l'Enfance, Paris, by Lange, Maxwell & Springer, London. 1952.

This publication is a collection of the papers read at a seminar on antibiotics organized in Paris in September, 1952, by the International Children's Centre. Fifty-four papers are included in full, the majority being concluded by a résumé of the discussion which followed each reading: 41 of the papers are written in French. The reports are grouped into four main sections: the action and use of antibiotics in pyogenic infections; the use of antibiotics in the treatment of tuberculosis; laboratory techniques and experimental work; and papers on the mode of action of the various antibiotics, their synergism and antagonism, and side-effects.

By the very nature of the seminar the views expressed are essentially personal and the results of the experience of the individual authors, but this collection forms an extremely valuable *vade mecum* for all who would seek guidance on the treatment of almost any disease in which antibiosis forms the main line of treatment.

Kinderärztliche Notfallfibel. 2nd edition. By B. DE RUDDER. (Pp. 164; DM. 13.50.) Stuttgart: Georg Thieme. 1953.

In this compendium, now appearing in its second edition, Professor de Rudder has produced a very useful 'aide' for both paediatrician and general practitioner on the medical and surgical emergencies of childhood. Each section is clearly set out under its appropriate headings, and incidence, pathology, diagnosis, prophylaxis and treatment are briefly discussed. It is to the author's credit that the reader easily gets a grasp of the essentials (both fundamental and practical) of each condition after reading the appropriate brief chapter. While respiratory catastrophes, septicaemia, coma, haemorrhagic syndromes, abdominal emergencies etc. are adequately discussed, one would like to see more space devoted to the chapter on poisoning.

This is a book which—if translated—would be a useful addition to the English literature.

Extrasystoles and Allied Arrhythmias. By DAVID SCHERF and ADOLF SCHOTT. (Pp. 531; 212 figures. £5 5s.) London: Heinemann. 1953.

Wenckebach in Vienna sowed the seed of this study which has come to fruition in London and New York after a generation. The book is learned, written in a plain easy style, and treats its subject mainly physiologically although history and clinical medicine are not stinted. The volume has been excellently turned out by the publishers and is nice to handle, but the practising paediatrician is unlikely to read it although he may use it for reference. If he wants to find out the incidence of extrasystoles in children he may consult a table with ten references (one to a paper in the *Archives of Disease in Childhood* by a member of the British Paediatric Association on page 457), and he may be interested to discover 'that extrasystoles in the foetus are not rare, that usually they are auricular in origin, often blocked, and that as a rule they tend to disappear soon after delivery'.

The Radiology of Bones and Joints. An Introduction to the Study of Tumours and other Diseases of Bone. 5th edition. By JAMES F. BRAILSFORD. (Pp. 875; over 725 figures. 90s.) London: J. & A. Churchill. 1953.

The fact that this book has reached its fifth edition in some 19 years in spite of the difficulties of publication and indeed of reading during the war period, is striking evidence as to its popularity. That it has met with this great demand is not really surprising when it is realized that it is the result of the author's 46 years of experience in a large and busy teaching hospital. During this time, also, the author has kept very closely in touch with the literature and has benefited from the writings of others. This is shown by the extremely large bibliography at the end of the book. Because of this, one would expect to find, as indeed one does, that it contains a wealth of material. It has been found necessary to extend the book over a hundred pages and to add a further hundred illustrations.

This edition follows the pattern of former editions, in that there are two complete sections, the first part being devoted to regional radiology and the second to abnormalities and pathology of bones and joints. There are, in effect, two books under the same cover. This is probably a virtue but it does give rise to some inherent difficulties of presentation. The first part deals with the various abnormalities as they occur in the different regions of the body. This approach necessarily leads to some reduplication which makes reading, in the sense of reading a textbook, somewhat trying, but used as a book of reference, which in fact it is, its value is very considerable. The illustrations in this section are well placed and closely follow the script. The second part is, really, a textbook on the radiology of bones and joints as distinct from a book of reference. The combination of the two sections in one volume means that the reader of the second section has constantly to refer back to illustrations occurring in the first part of the book and this can be indeed very irritating. This irritation might, to come extent, be alleviated by giving the number of the page on which the illustration occurs rather than the figure number.

In a work of this magnitude, however, these are very minor criticisms and there is no doubt that those who are interested in bone and joint pathology and the treatment of bone and joint diseases will be the poorer if they do not have it upon their shelves. As is to be expected of the House of Churchill, the whole production of this book is of very high quality, the paper is good, the type is pleasing and the illustrations are very well reproduced.

Advice to the Expectant Mother. 10th edition. By F. J. BROWNE. (Pp. 48; one figure. 1s.) Edinburgh and London: E. & S. Livingstone. 1953.

The tenth edition of this booklet has now appeared, and this in itself is a reflection of its deserved popularity. One particular criticism is the curious inclusion of a paragraph

on cancer of the womb; this seems out of place in a book for expectant mothers. Not all paediatricians will agree with the advice on such early training of the bowel and bladder in the infant, the early feeding of the premature infant with sugar water, or treatment of constipation in the infant with magnesia or liquid paraffin. These, however, are minor criticisms of a clear, well indexed, inexpensive booklet. Expectant mothers will welcome this new edition.

Joint UN/WHO Meeting of Experts on the Mental Health Aspects of Adoption. (Pp. 19. 1s. 3d.) Geneva: World Health Organization (London: H.M. Stationery Office). 1953.

As the title of this publication suggests a considerable emphasis is placed on the mental adjustments necessarily involved in any case of adoption.

The main sections of the pamphlet deal with the nature and purpose of adoption, the status of children in need of adoption, the child and his future, the adopting parents and the selection and training of staff concerned with adoption procedures. These aspects of the problem are dealt with in relation to the situation usual in western communities which do not always readily accept the unmarried mother.

It is difficult to know quite what public this pamphlet was written for as it does not aspire to any scientific heights and the social worker is not likely to be unaware of its contents.

BOOKS RECEIVED

(Review in a later issue is not precluded by notice here of books recently received.)

Year Book of Pediatrics 1953-1954 Series. Edited by Sydney S. Gellis and Isaac A. Abt. (Pp. 435; 114 illustrations. 45s; $6.00.) The Year Book Publishers, Chicago; distributed in Great Britain by Interscience Publishers. 1953.

Diagnosis of Acute Abdominal Pain. By William Requarth; Foreword by Warren H. Cole. (Pp. 243; 79 illustrations. 38s; $5.00.) The Year Book Publishers, Chicago; distributed in Great Britain by Interscience Publishers. 1953.

A Synopsis of Children's Diseases. By John Rendle-Short. (Pp. 620; illustrated. 32s. 6d.) Bristol: John Wright & Sons. 1954.

Die Mund und Rachenkrankheiten: Klinik und Therapie. By C. R. Griebel. (Pp. 140; 42 illustrations. DM. 29.-) Stuttgart: Georg Thieme Verlag. 1954.

Manuel Practique de Vaccination par le B.C.G. By R. Mande; Foreword by Robert Debré. (Pp. 200; 13 plates including four in colour. Fr. frs. 950.-) Paris: Masson et Cie. 1954.

Pediatric Clinics of North America (Cardiovascular Diseases). (Pp. viii+279; 96 illustrations. £4 10s. per annum in Great Britain and Eire, £5 5s. elsewhere.) London: W. B. Saunders. February, 1954.

Clinical Management of Behavior Disorders in Children. By Harry Bakwin and Ruth Morris Bakwin. (Pp. 495; 14 illustrations. 50s.) London: W. B. Saunders. 1953.

A Guide to the Film **"A Two-Year Goes to Hospital".** (Pp. 20; illustrated.) London: Tavistock Publications Ltd. 1953.

Infant Feeding and Feeding Difficulties. 2nd ed. By Philip Evans and Ronald MacKeith. (Pp. x+277; 66 illustrations. 12s. 6d.) London: J. & A. Churchill. 1954.

Tuberculosis in Childhood and Adolescence. By F. J. Bentley, S. Grzybowski and B. Benjamin; Preface by Sir Robert A. Young, Foreword by Wilfrid Sheldon. (Pp. 272; illustrated. 30s.) London: National Association for the Prevention of Tuberculosis. 1954.

Duxième Congrès International d'Hygiène et de Médicine Scolaires, Lyon, 9, 10, 11 et 12 juillet, 1952. I.—Tuberculose à l'École; II.—La Scolarité des Retardés; III.—Autres Questions. (Pp. 504; illustrated. Fr. frs. 3,000.-) Paris: G. Doin et Cie. 1953.

Klinische Darmbakteriologie für die Ärztliche Praxis. By Tr. Baumgärtel. (Pp. viii+130. DM.14.40.-) Stuttgart: Georg Thieme Verlag. 1954.

Gesundheit durch Krankheit. Das Rätsel der Immunität. By Hans-Joachim Flechtner. (Pp. 346; 30 illustrations.) Dusseldorf: Econ-Verlag GMBH. 1954.

The Handicapped Child. Letters to Parents. By Karl Konig. (Pp. 19. 1s. 6d.) London: New Knowledge Books. 1954.

Auditory Disorders in Children. A Manual for Differential Diagnosis. By Helmer R. Myklebust. (Pp. xiii+367. $6.00.) New York: Grune & Stratton. 1954.